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.2024-01
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 31.03.2024
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.2024-01
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 31.03.2024
Тираж 100 экз. Отпечатано в типографии Print.Formula
www.print-formula.ru

MEDICAL ETHICS **1, 2024**
МЕДИЦИНСКАЯ ЭТИКА

Contents
Содержание

SCHOOL OF RESEARCH ETHICS. AXIOLOGY OF BIOETHICS AND CHALLENGES OF TECHNOLOGICAL DEVELOPMENT

Firsov DE ✉

Yaroslavl State Medical University, Yaroslavl, Russia

Intensive development of modern science expands the scope of bioethical issues. Debates on ethical aspects of bioinformatics, neurotechnology, genetics, bioeconomics, ethics of preclinical and clinical trials are actively developing. Axiology of bioethics is of particular relevance. It is the structure of valuable categories that determines the priorities of 'human science' development taking into account the historical experience of interaction between a person and community, and criteria of civilized changes in the actual and perspective (prognostic) sense. Development of bioethical axiology is influenced by the challenges of technological development of the current decade, the issues that objectively demand a reaction on the part of the state and society. One of the main tasks of modern bioethics is to develop bioethical thinking, and grounds for using bioethical axiology in the scientific process. Health axiology, which represents a fixed conscious attitude to the issues of health developed during the academic process to be subsequently used during a labor process, is practical expression of bioethical thinking. Bioethical dialogue is essential as it urges young perspective specialists to examine novel bioethical scientific issues and achieve technological country-specific goals. Focus on young scientist's potential totally corresponds to the cross-cutting goal of axiological, prognostic and educational tasks of bioethics. Bioethical thinking is developed based on the experience of the school of ethics of scientific research, which is an educational project intended for young Russian researchers.

Keywords: bioethics, axiology, health, bioethical thinking, research process

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

Received: 05.02.2024 **Accepted:** 25.02.2024 **Published online:** 10.03.2024

DOI: 10.24075/medet.2023.035

ШКОЛА ЭТИКИ НАУЧНЫХ ИССЛЕДОВАНИЙ. АКСИОЛОГИЯ БИОЭТИКИ И ВЫЗОВЫ ТЕХНОЛОГИЧЕСКОГО РАЗВИТИЯ

Д. Е. Фирсов ✉

Ярославский государственный медицинский университет, Ярославль, Россия

Интенсивное развитие современной науки расширяет диапазон биоэтических проблем. Активно развивается дискуссия по вопросам этических аспектов биоинформатики, нейротехнологии, генетики, биоэкономики, этики доклинических и клинических исследований. В связи с этим приобретает особую актуальность тема аксиологии биоэтики — структуры ценностных категорий, определяющих приоритеты развития «наук о человеке» с учетом исторического опыта взаимодействия личности и социума, критериев цивилизационных изменений в актуальном и перспективном (прогностическом) значении. На развитие биоэтической аксиологии оказывают влияние вызовы технологического развития текущего десятилетия, проблемы, объективно требующие реакции со стороны государства и общества. Одной из важнейших задач современной биоэтики является формирование биоэтического мышления, оснований применения биоэтической аксиологии в научно-исследовательском процессе. Практическим выражением биоэтического мышления является аксиология здоровья — закрепление осознанного отношения к проблемам здоровья, формируемого в учебном процессе с целью дальнейшего применения в трудовом процессе. Биоэтический диалог важен для решения задач привлечения молодых перспективных специалистов к изучению новых биоэтических вопросов науки, к достижению поставленных на уровне страны технологических целей. Нацеленность на потенциал молодых ученых полностью соответствует сквозной цели аксиологических, прогностических и образовательных задач биоэтики. Формированию биоэтического мышления способствует опыт Школы этики научных исследований — образовательного проекта для молодых российских исследователей.

Ключевые слова: биоэтика, аксиология, здоровье, биоэтическое мышление, исследовательский процесс

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

Статья поступила: 05.02.2024 **Статья принята к печати:** 25.02.2024 **Опубликована онлайн:** 10.03.2024

DOI: 10.24075/medet.2023.035

Evolution of modern bioethical discourse that reflects the trajectory of scientific and humanitarian knowledge development rests with the axiological potential of major principles of ethical regulation of scientific and technological progress.

Axiology of bioethics is the structure of valuable categories, which determine the priorities of developing the 'human science' taking into account the historical experience of interaction between the personality and society, criteria of civilized changes in the actual and perspective (prognostic) sense.

Development of bioethical thinking and grounds for the practical use of bioethical axiology during the research process is one of the most important tasks of modern bioethics.

Axiological bioethical interval arranges both general-purpose issues including the issues of correlation between moral, ethical and legal imperatives of the ethical choice, 'health axiology', other categories and their value in the practical activity of the specialist, and applied and deontological issues.

The problems, which are solved by modern bioethics, are based on 'eternal dilemmas', which are inevitably faced by a person during every stage of science and technology evolution. The issues of freedom and responsibility of a person, 'sense of existence', meanings of 'justice', 'due' and 'benefit' categories formed a subject area of ethics as 'ethos' philosophy, which is a detailed reflection of social reality.

Development of social relations required codification and classification of universal values, including the collective reception of historical experience of moral and legal regulations of the professional activity involving the area of medical knowledge and science as a whole.

Since the days of Aristotle (Nicomachean Ethics), there existed a tradition, in accordance with which 'wisdom' was defined as 'scientific knowledge and comprehension of things, which are the most valuable by nature'. Thesis of Potter VR, who was a founder of the bioethical concept (Bioethics: Bridge to the Future, 1971), continued this thought that reflected sociocultural realities of the XX century as follows: ''Mankind is urgently in need of a new wisdom that will provide <knowledge of how to use knowledge> for man' s survival and for improvement in the quality of life… that would combine two most essential and extremely necessary elements such as the science of biology and human values. I coined a new term "bioethics" to denote it' [1]. The methods of the 'science of biology' suggested by Potter VR formed the basis of the modern bioethical discussion and experience of implementing the ethical principles in practice.

By the middle of the XX century, the global community went through several self-determination landmarks regarding establishment of fundamental principles of global ethics. The Nuremberg Code, the provisions of which were formulated while assessing the consequences of World War II and that still remain relevant in the XXIth century, belonged to one of the first and most fundamental steps in this direction [2]. Another essential step of establishing parameters of research ethics and human experiments is represented by the Declaration of Helsinki (1964) developed by the World Medical Association as a code for ethical principles for a medical community. The relevance of this international instrument, the sixtieth anniversary of the adoption of which will be celebrated in 2024, is supported by modern practice.

Unlike the codes that generalize the previous experience of science development, Potter VR concludes that a global strategy and 'scientific and philosophical concept' of social progress built on 'comprehension of long-term wisdom' are required.

The starting point of bioethics asserts that it is necessary to develop the technologies taking into account the factor of 'dangerous knowledge', which is 'accumulated more rapidly than the wisdom required to control it'. Developing the idea of Aristotle, Potter VR asserts that 'science implies moral knowledge, but it is not wisdom yet. Wisdom means to know how to use the achievements of science and how to balance the science with other areas of human knowledge to achieve collective wisdom'. 'Until part of social attempts is not devoted to the search of wisdom, scientific research won't add value to the society' [1].

According to Potter VR, 'bioethics should strive to reproduce wisdom, recognizing existence of the biological world and human nature and comprehending how the obtained knowledge can be used to reach the social value'. The realistic view of human possibilities 'could not be wisdom at all if not supported by the humanistic and ecological world view'.

Thus, the bioethical strategy of Potter VR is postulated as a scientific concept and revealed both as the worldview, and as the axiological paradigm, which is a pattern of target setting and searching solutions.

Criteria of human life and health determined in the WHO Constitution and reflected in the definition of article 2 of Federal Law as of 21.11.2011 No. 323-ФЗ (as amended on 25.12.2023) 'On fundamental healthcare principles in the Russian Federation (with amendments and additions entering into force since 05.01.2024): 'Health is physical, mental and social human well-being, when diseases and disorders of the functions of organs and systems of the body are lacking' constitute the basis of the axiological interval of bioethics.

Thus, basic values of life quality include a set of physical health parameters, criteria of mental and social well-being, factors of spirituality, mobility and environment that constitute an integrative value of life quality ranging from the maximum satisfaction to the lower boundary of the optimum denoting the minimal permissible level of the functional correlation of life quality indices for a certain individual.

A ratio of additional factors that influence the value of human quality of life and health criteria, definition of the optimum (morality and law) lower border, and requirements to implementation of human rights set by the educational and professional standards should be taken as a separate issue.

Challenges of technological development of the current decade set in the Order of the Government of the Russian Federation s of May 20, 2023 No. 1315-p, influence bioethical axiology [3]. Challenges of technological development is a set of problems, threats and possibilities in the area of development and implementation of technologies, that calls for a reaction from the state and society. The complexity and scope of the problems make it impossible to solve, eliminate or implement without structural changes due to an increase in resources only. The concept of technological development of Russia until 2030 includes ten 'end-to-end technologies' and eight directions of industrial development, including artificial intelligence and manufacture of medicinal agents.

Use of systemic processes of science and manufacturing system development is a way to develop the Russian manufacture. The functions of state institutions include establishing and ensuring transparent and stable regulatory rules of behavior and interaction of subjects of technological development, strategic planning and target setting. Improvement of scientific directions and implementation of results into practice means that 'there is a need in a systemic change of approaches to scientific and technological development of the country'. These processes expect optimization of the bioethical paradigm that reflects a real progress achievement.

Creation of technological conditions for the social and economic development of the country in accordance with the national purpose of development of the Russian Federation until 2030 and national interests provides for the creation of own scientific, personnel and technological base of critical and cross-cutting technologies, including the ones that provide for manufacture of high-technology products, including medicines and medical equipment, technology of new materials and substances, their modeling and development.

New trends of scientific research alter the expanding horizon of the bioethical regulation sphere, constitute the subject of bioethical discourse and determine the vector of bioethical axiology.

Modern ethics embraces a wide range of issues which are pressing for the technological civilization level in the XXI century. They include ethical issues of productive health and regenerative medicine, ethics of donorship, bio- and nanotechnologies, accessibility to medical aid, environmental ethics and diversity issues. Ethical aspects of bioinformatics, neurotechnology, biomedical law and bioeconomics have been of a great importance during the last decades. The role of bioethical issues of genetics increases significantly. During the General Conference of the 42nd session of UNESCO (Paris, 2023), there was a need in normalization of ethical aspects of neurotechnology and associated health threats.

The common basis for bioethical discussions consists of ethical aspects of preclinical and clinical trials, including the issues of confidential personal data, objective trial-related information, compliance with the principle of informed voluntary consent, trial risks and associated compensation of health harm.

The vector of bioethical research in Russia includes general target setting of science and technology development within the Strategy of science and technology development of the Russian Federation approved by the Presidential Decree of the Russian Federation as of December 1, 2016 No. 642 'On the strategy of science and technology development in the Russian Federation' in conjunction with the national development purposes.

It is necessary to mention the value of bioethical dialogue regarding involvement of science to deal with new bioethical science issues, and achievement of country-specific technological targets of young perspective specialists. On November 28–30, 2023, the 3rd Congress of Young Scientists was held on Sirius federal platform where a session entitled 'Scientific search and ethical and legal issues of research activity' was organized as a working group meeting on regulatory legal environment and bioethics in the sphere of genetic technologies.

Focus of young scientists on the potential totally corresponds to the cross-cutting goal of axiological, prognostic and educational bioethical ethics.

Potter VR noticed that 'a new generation of scientists should be formed on the basis of broad complex education in the area of fundamental human trials, humanitarian and social sciences', which are combined to 'generate wisdom' and solve 'remote and long-term human issues'. 'The study purpose… will be to create the concept of order using the categories of morality, traditions, customs and law'. 'The obtained results should be used in the educational system as soon as possible'.

The main task of bioethical research is to develop bioethical thinking. Bioethical thinking means conscious use of bioethical axiology in the scientific process. Bioethical thinking means successive and continuous conceptual correlation of professional knowledge and its such axiological periphery as 'knowledge about knowledge'. The correlation is determined using a strict bioethical argumentation.

During formation of bioethical ideas, it is important to repudiate the conceptual correlation between bioethical 'knowledge (wisdom) about knowledge' and scientific knowledge. To implement this, it is necessary to take into account the influence of psycho-cultural perception factors.

For this, it is necessary to prevent the reduction of bioethical knowledge into the optional information, overcome the artificial gnoseological barrier, that virtually separates biology from bioethics using the scientific status, and conceptual integration of bioethical model into gnoseological the pattern of scientific ideas [4].

Health axiology — consolidation of conscious attitude to health issues developed during the academic process for the purpose of subsequent use during the labor process — is practical implementation of bioethical thinking.

Formation of a complex idea about ethical and deontological basis of medical and research ethics is basic when a reasonable attitude to health issues is being fixed. Complex analysis of professional demands, which a medical professional and researcher comes across during a daily life, is an aspect of the educational function of modern bioethics as an academic discipline.

Moral health and capacity for active mercy are essential in comprehension of health within the tradition of the national medical school. Uglov FG wrote: 'be rational about the health you were given at birth, and appreciate this beautiful and precious gift'. According to St Luke (Voyno-Yasenetsky), 'the purpose of life is perfect love and impeccability. To achieve this, we need to purify our heart continuously'. Relevance of this approach is confirmed with the initiative on consolidation of efforts from representatives of medical education and practical healthcare, secular society and confessional alliances solving general pressing ethical tasks [5].

Correlation of bioethical theory and practice is seen through the processual bioethical model with a phased sequence of responsibility disclosure [6]. In particular, the objective assessment of the need in planning the research is associated with the issues of biobanking and bioanalytics development [7].

The cross-cutting nature of ethical principles is seen in the context of ethics of goals and ethics of means. Axiological succession of the research process and following the priorities prevent the incongruity of conceptual ideas and instrumental tasks of the research.

Ethics is a regulator of research activity in close interrelation with law. In historical aspect, ethical systems (moral norms) with potential axiological extrapolation based on objectivity, applicability and specificity were used as the basis of legal regulations. Modern international agreements and national legislation regulate both general issues of ethical regulation, and separate aspects of rendering medical aid and research practice. Legislation of the Russian Federation provides for legal support of development and improvement of ethical regulations in all directions of research activities. Collections of materials are published to systematize and update the data [8, 9].

Search of answers to ethical questions that arise during the research process is not limited to the formal sphere only and constitutes the essential foundation of the moral self-determination of the scientist. In the XXI century, the following words of Lomonosov MV are still valid: 'Explore all the time what is great and mighty!'

CONCLUSIONS

Modern bioethics rests upon the pressing achievements in the area of naturalistic and sociocultural knowledge providing human life and society values and well-being.

The 'interdisciplinary status' reflects the axiological and prognostic potential of bioethics as a developing perspective scientific direction.

The bioethical concept in Russia sums up the world-view value priorities of the scientific community as per the legislation and taking into account the historical experience of Russian healthcare, general target setting of science and technology development, criteria of progress in the actual and perspective (prognostic) sense.

Bioethical thinking is a conscious use of bioethical axiology in scientific research, healthcare and social practice based on the successive and continuous sense correlation between professional knowledge and its axiological periphery ('knowledge about knowledge').

Bioethical discourse of scientific knowledge helps to overcome cognitive rigidity and improves formation of reasonable grounds of specialists' proactivity.

Consolidated moral efforts of everyone interested in progressive science and introducing achievements of science into practice are essential for subsequent development of bioethics. Experience of the School of Research Ethics — educational project for young Russian scientists — contributes to that to a large extent [10].

References

1. Potter VR. Bioetika: most v budushcheye. 2002; 216 s. Russian.
2. Chuchalin AG, Sayamov Yu N. K 75-letiyu nachala Nyurnbergskikh protsessov i sozdaniya Nyurnbergskogo kodeksa: global'noye znacheniye i neprekhodyashchiye uroki. Meditsinskaya etika. 2021; (1): 6–11. Russian.
3. Rasporyazheniye Pravitel'stva Rossiyskoy Federatsii ot 20.05.2023 № 1315-r. Ofitsial'noye opublikovaniye pravovykh aktov. Available from URL: http://publication.pravo.gov.ru/document/0001202305250050 (accessed 26.01.2024) Russian.
4. Firsov DYe, Aybabina Ye V. Psikhokul'turnyye faktory formirovaniya bioeticheskoy kompetentsii u studentov meditsinskogo vuza. V sbornike: Voprosy otechestvennoy i zarubezhnoy istorii, politologii, sotsiologii, filosofii, obrazovaniya. Materialy konferentsii. Yaroslavl': Yaroslavskiy gosudarstvennyy pedagogicheskiy universitet im. K. D. Ushinskogo, 2022; 219–224. Russian.
5. Khokhlov AL, Zhbannikov PS, Zarov AYu, Firsov DYe, Shkurankov AV, Makarov SV. Obrazovaniye, zdorov'ye, miloserdiye. Podgotovka sester miloserdiya v Yaroslavskom meditsinskom universitete. Meditsinskaya etika. 2023; (4): 4–6. Russian.
6. Tomashov VV, Firsov DYe. Protsessual'naya bioeticheskaya model' realizatsii professional'noy otvetstvennosti. V sbornike: Aktual'nyye problemy sovershenstvovaniya vysshego obrazovaniya: materialy konferentsii. YarGU, 2018; 392–394. Russian.
7. Orlova NV, Suvorov GN, Gorbunov KS. Etika i pravovoye regulirovaniye ispol'zovaniya bol'shikh baz dannykh v meditsine. Meditsinskaya etika. 2022; (3): 4–9. Russian.
8. Pantuyev PA, Gumarova AN. «Biblioteka bioetiki»: vklad v razvitiye obrazovaniya (Retsenziya na mnogotomnoye izdaniye) M.: Veche, 2019–2022. T. 1–10. Meditsinskaya etika. 2023; (2): 9–13. Russian.
9. Firsov DYe, Miroshnikov AYe, Pozdnyakov NO. Obzor rukovodstva dlya komitetov po etike «Eticheskaya ekspertiza biomeditsinskikh issledovaniy: prakticheskiye rekomendatsii» (tret'ye izdaniye, ispravlennoye i dopolnennoye). Pod obshchey redaktsiyey A. L. Khokhlova. Meditsinskaya etika. 2022; (1): 10–13. Russian.
10. Shkola etiki nauchnykh issledovaniy. Available from URL: https://ethic.nriph.ru. (accessed 03.02.2024). Russian.

Литература

1. Поттер В. Р. Биоэтика: мост в будущее. 2002; 216 с.
2. Чучалин А. Г., Саямов Ю. Н. К 75-летию начала Нюрнбергских процессов и создания Нюрнбергского кодекса: глобальное значение и непреходящие уроки. Медицинская этика. 2021; (1): 6–11.
3. Распоряжение Правительства Российской Федерации от 20.05.2023 № 1315-р. Официальное опубликование правовых актов. Режим доступа: [Электронный ресурс]. URL: http://publication.pravo.gov.ru/document/0001202305250050 (дата обращения 26.01.2024).
4. Фирсов Д. Е., Айбабина Е. Potter Психокультурные факторы формирования биоэтической компетенции у студентов медицинского вуза. В сборнике: Вопросы отечественной и зарубежной истории, политологии, социологии, философии, образования. Материалы конференции. Ярославль: Ярославский государственный педагогический университет им. К. Д. Ушинского, 2022; 219–224.
5. Хохлов А. Л., Жбанников П. С., Заров А. Ю., Фирсов Д. Е., Шкуранков А. В., Макаров С. В. Образование, здоровье, милосердие. Подготовка сестер милосердия в Ярославском медицинском университете. Медицинская этика. 2023; (4): 4–6.
6. Томашов В. В., Фирсов Д. Е. Процессуальная биоэтическая модель реализации профессиональной ответственности. В сборнике: Актуальные проблемы совершенствования высшего образования: материалы конференции. ЯрГУ, 2018; 392–394.
7. Орлова Н. В., Суворов Г. Н., Горбунов К. С. Этика и правовое регулирование использования больших баз данных в медицине. Медицинская этика. 2022; (3): 4–9.
8. Пантуев П. А., Гумарова А. Н. «Библиотека биоэтики»: вклад в развитие образования (Рецензия на многотомное издание) М.: Вече, 2019–2022. Т. 1–10. Медицинская этика. 2023; (2): 9–13.
9. Фирсов, Д. Е., Мирошников, А. Е., Поздняков, Н. О. Обзор руководства для комитетов по этике «Этическая экспертиза биомедицинских исследований: практические рекомендации» (третье издание, исправленное и дополненное). Под общей редакцией А. Л. Хохлова. Медицинская этика. 2022; (1): 10–13.
10. Школа этики научных исследований. Режим доступа: [Электронный ресурс]. URL: https://ethic.nriph.ru. (дата обращения 03.02.2024).

CONNECTING LINKS OF HISTORY. YAROSLAVL AND SERGEY SPASOKUKOTSKY

Eregina NT ✉

Yaroslavl State Medical University, Yaroslavl, Russia

Biography of Sergey Spasokukotsky, the outstanding Russian surgeon, is closely related to the Yaroslavl Territory. He spent his childhood in the Danilovsky region, coming from a large and friendly family of a zemstvo doctor. In 1880–1888, he studied at the Men's Gymnasium after his family had moved to Yaroslavl. The building now belongs to the Yaroslavl State Medical University where a representative of his scientific school, Professor Busalov AA, worked decades later. Life and activity of Sergey Spasokukotsky represent a bright example of unselfish service to medicine. Being a graduate of the Emperor's Moscow University, he had a chance to continue his medical career in Moscow but went to the province where he worked as a zemstvo doctor for many years, actively implementing advance achievements of medicine into abdominal surgery, neurosurgery, pulmonary surgery, creating novel and modifying available surgeries. S. Spasokukotsky and his student developed an affordable and effective method of preparing a surgeon's hands for a surgery with 0.5% ammonia solution (method by Spasokukotsky and Kochergyn). The scientific and practical activities of Sergey Spasokukotsky resulted in the development of a large scientific school with an ultimate scientific social responsibility, originality, great depth and boldness while solving the issues of surgical pathology.

Key words: Sergey Spasokukotsky, zemstvo medicine, surgery, asepsis and antiseptics, Yaroslavl State Medical University

✉ **Correspondence should be addressed:** Natalia T. Eregina
Revolutsionnaya Str., 5, Yaroslavl, 150000, Russia; ereginant@mail

Received: 05.03.2024 **Accepted:** 10.03.2024 **Published online:** 26.03.2024

DOI: 10.24075/medet.2024.004

ИСТОРИИ СВЯЗУЮЩИЕ НИТИ. ЯРОСЛАВЛЬ И СЕРГЕЙ ИВАНОВИЧ СПАСОКУКОЦКИЙ

Н. Т. Ерегина ✉

Ярославский государственный медицинский университет, Ярославль, Россия

Биография выдающегося отечественного хирурга Сергея Ивановича Спасокукоцкого тесно связана с Ярославским краем. Здесь, в Даниловском районе, в большой и дружной семье земского врача прошло его детство. После переезда семьи в Ярославль, в 1880–1888 гг. он обучался в мужской гимназии. Здание, где она размещалась, ныне принадлежит Ярославскому государственному медицинскому университету, в котором десятилетия спустя работал один из представителей его научной школы — профессор А. А. Бусалов. Жизнь и деятельность С. И. Спасокукоцкого являются ярким образцом бескорыстного служения медицине. Выпускник Императорского Московского университета, имевший возможность продолжить врачебную карьеру в Москве, он уехал в провинцию, где многие годы работал земским врачом, активно внедряя передовые достижения медицины в абдоминальную хирургию, нейрохирургию, легочную хирургию, создавая новые и модифицируя уже практикующиеся операции. С. И. Спасокукоцкий совместно со своим учеником разработал доступный и эффективный способ подготовки рук хирурга к операции с помощью мытья 0,5%-ным раствором нашатырного спирта (способ Спасокукоцкого–Кочергина). Итогом научно-практической деятельности С. И. Спасокукоцкого стало создание большой научной школы, отличающейся предельной научной добросовестностью, оригинальностью, большой глубиной и смелостью в решении вопросов хирургической патологии.

Ключевые слова: С. И. Спасокукоцкий, земская медицина, хирургия, асептика и антисептика, Ярославский государственный медицинский университет

✉ **Для корреспонденции:** Наталья Тимофеевна Ерегина
ул. Революционная, д. 5, г. Ярославль, 150000, Россия; ereginant@mail.ru

Статья поступила: 05.03.2024 **Статья принята к печати:** 10.03.2024 **Опубликована онлайн:** 26.03.2024

DOI: 10.24075/medet.2024.004

Sergey Spasokukotsky was one of the most outstanding Russian surgeons whose biography is closely connected with the city of Yaroslavl. A plaque bearing his name decorates the facade of the main building of the Yaroslavl State Medical University. 'Sergey Spasokukotsky, Academician of the Academy of sciences of the USSR, Laureate of the State Youth Award, studied here, at the former Men's Gymnasium, in 1880–1888'.

In 50 years, his student, one of the brightest representatives of Spasokukotsky Surgical School, Professor Aleksey A. Busalov, M.D., recognized by the biographical commission of the Dmitrovsky region as the 'Best XX Century Citizen of the Dmitrovsky region in the "Doctor" nomination' will be working at the building. In 1938–1947, Busalov AA was the head of the medical and sanitary management of the Kremlin. While working in Yaroslavl for some years, he emerged as a wonderful organizer, academic advisor, and experienced surgeon.

Sergey Spasokukotsky was born on June 10, 1870, in Kostroma, an old Russian city, in the family of Ivan V. Spasokukotsky, who was a zemstvo doctor. His grandfather was a rural parson of Spasskoye village on the Kukot river. This is where the original surname originated from. His father owned the Smyslovo estate (Danilovsky district) in the Yaroslavl province. The estate was inherited from his wife who died early of tuberculosis but managed to give birth to four children during a very short and happy period of their family life. The family spent every year in Smyslovo. In 1874, his father retired and settled in Yaroslavl surrounded by his family. Initially, they used to rent an apartment on the Volga embankment and then moved to the center of the old city (Ushinskogo Str., 12) that preserved to this day.

When Sergey was nine years old, he studied at the Men's Gymnasium, which was in 1880 relocated to the place where now the main building of the Yaroslavl State Medical University is placed. Reports of academic achievements are held in the State Archive of the Yaroslavl Territory. Some of them have been there since the college years of Spasokukotsky. It should be noted that Sergey has had an excellent academic performance since the very beginning of studying at the

gymnasium. The magazine had a specific rating of students. Thus, Spasokukotsky had the best success and diligence in a class of 44 [1]. Popovich PP, Associate Professor of the department of morbid anatomy who studied biography of Spasokukotsky and documents of the Yaroslavl Archives and Moscow University wrote as follows: 'the available data make it possible to conclude that in junior school Sergey had a clear predominance of excellent grades. After the fourth year of education, good and satisfactory grades appeared. A high school certificate is being kept in documentary funds of the Moscow University. It contains no satisfactory grades, three excellent grades, whereas all the other grades were good. His behavior was commonly excellent' [2]. In different years, the gymnasium was completed by Sergey's brothers — Nikolay (1887) and Vladimir (1891).

The example of his father who has devoted his entire life to zemstvo medicine was defining in Sergey's profession. In 1888, he entered the Medicine Faculty of the Moscow Emperor's University. During that time, its teachers were outstanding scientists, doctors who left a bright trace in the history of higher medical institution and history of Russian medicine such as anatomist Zernov DN, surgeons Sklifosovsky NV, Bobrov AA, Dyakonov PI, bacteriologist Gabrichevsky GN, therapists Eltsynsky VI, Golubov NV, botanist Timirzyaev KA, pediatrician Filatov NV, neurologists Kozhevnikov AYa and Darkshevich LO, psychiatrist Korsakov SS, therapist Zakharyin GA, hygienists Erisman FF, Ignatyev VE, etc.

The system of preparation used at the medical faculty of the Moscow University in the second half of the XIX century taught students the art of medical science. The reform of clinical teaching that introduced three consecutive and closely interrelated stages of clinical preparation (propedeutic, theoretical, hospital) played a decisive role in this. Their step-by-step mastering made it possible for students to study the basis of clinical medicine and acquire own experience of medical practice. As soon as the University has been graduated, they were ready for the practice [3].

In summer 1893, on the eve of state graduation exams, Sergey Spasokukotsky became part of the Red Cross detachment struggling with the epidemic of typhus that raged in many Russian villages. In the end of the XIX century, Russia was one of the first countries in the world in terms of the prevalence of typhus. The disease was mainly developed among the poor. Spasokukotsky became ill with typhus while saving patients. As a result, he passed his graduation exams only after he had recovered in autumn 1893. The mediciner oath signed by Spasokukotsky SI is of interest. It is similar to the up-to-date medical oath, and until 1917, all graduates of the medical faculty were called 'mediciners'.

'Accepting the rights of a doctor with deep appreciation and understanding the importance of obligations incumbent upon me with the title, I promise not to darken the honor of the profession I am now becoming a part of. I promise to help those suffering at any time; keep family secrets sacred and not to misuse the trust I've been given. I promise to continue studying medicine and contribute to its prosperity informing the men of science of anything that will be discovered by me. I promise not to make and sell any secret preparations. I promise to be just to my colleagues and not insult their personalities; however, if a patient's benefit requires so, I can tell truth directly and impartially. In essential cases, I promise to follow the advice of doctors who are more educated and experienced; whenever I am summoned for a meeting, I will remember about their merits and efforts' [4].

By the Decision of Professor Council, S. Spasokukotsky was left at the University as a Supervising Resident of the Hospital Surgical Clinic of Prof. Levshin to prepare for subsequent scientific activity. Its academic advisor was an extraordinary personality. He worked at Saint-Petersburg Medical Academy, had internship abroad, was both professor and dean of the medical faculty of the Kazan University, and participated in the Russo-Turkish War. In 1893, when S. Spasokukotsky graduated from the University, Prof. Levshin was shifted to the Moscow University as full-time Professor of hospital surgery department and Director of Hospital Surgical Clinic. In 1903, when Levshin LL retired, he used his private contributions to establish the Institute to study ways of cancer treatments (it is called P. A. Herzen Moscow Oncological Research Institute today) [5].

Sergey spent three busy years working on the thesis. He acquired the skills of independent work as a surgeon outside the clinic. A young surgeon had no conditions for development there. No payment was offered for the part-time residency, and he had to search for earnings. While working on the thesis, he also applied for the seasonal job (May-September) of a doctor at the Arkhangelsk Railroad that was under construction. Here, an extensive field of medical practical activity could be covered as surgeons, infectious disease doctors, therapists, traumatologists and administrators were in need.

In 1897, S. Spasokukotsky went to the Greek-Ottoman War as part of Red Cross detachment consisting of some former clinical residents and leading lights in medicine (Sklifosovsky NV, Bobrov AA and Levshin SI). We still have his letters where tough events of those times were described. He used the methods of aseptics, antiseptics, and 8-shaped removable sutures, which subsequently became part of the surgical practice.

Having returned from the front in September 1897, S. Spasokukotsky decided to go to Smolensk where he worked as a surgeon at the provincial zemstvo hospital. He also completed his MD thesis entitled 'Osteoplasty in limb amputations' that was successfully defended in 1898. S. Spasokukotsky's thesis was printed in a Smolensk typography and contained 158 pages of text with tables and photos. During the practice, he came back to the topic many times [6].

S. Spasokukotsky worked at Smolensk zemstvo hospital from 1897 to 1911. Having an outstanding organizational skill, he could rebuild the entire surgical work actively implementing the novel achievements of medicine (antiseptics and aseptics) into practice. This allowed to perform herniotomies, which were seldom used before due to a large number of complications. During the 1st Congress of Russian Surgeons (1900), S. Spasokukotsky reported 257 herniatomies performed at his clinic, and 623 cases of herniatomy done in two years (during another Pirogov Congress) [7].

When the Russo-Japanese war started, S. Spasokukotsky headed the Red Cross detachment and went to the Far East following the call of the heart. He operated and took care of the wounded and acted as a surgeon for the local people. He wrote as follows: 'The view of the badly wounded people makes you forget yourself. You try to be useful. Yesterday, for instance, I spent the entire evening shaving and washing the patients (they were very dirty and covered with parasites)… The useless and dark war is a nightmare just as the forces that have involved us in it' [8].

Having returned from war in 1905, S. Spasokukotsky immersed himself in the work. Being a surgeon of a provincial zemstvo hospital, he actively developed surgery of stomach diseases, familiarized doctors with the original view on a widely distributed pathology of those times (ileus) stating that it is a hungry person's disease.

The talented surgeon became widely known to the Russian medical community. It is no surprise that he was invited to be the head of the department of operative surgery and regional anatomy in 1911, and department of hospital surgery of the Saratov University in 1913. During that period, he was actively working almost in all fields of surgery (abdominal surgery, neurosurgery, pulmonary surgery) establishing new and modifying already existing operations. S. Spasokukotsky developed an affordable and effective way of preparing a surgeon's hands for an operation with 0.5% ammonia solution (the method of Spasokukotsky-Kochergin). He was the first person who used a blind suture after the surgical treatment of wounds in the skull and abdomen and skeletal extension while treating fractures. During the First World War, he was the head of three departments of the Saratov University, delivered three lecture courses, and had surgeries in two clinics and a war hospital. Having accepted the socialistic revolution without any hesitation, he organized a hospital in Saratov in 1918 to treat the wounded Red Army soldiers making it possible for them to return to work. He also became the first director of the hospital. In 1945, the Research Institute of Traumatology and Orthopedics was established on the basis of the hospital [9].

S. Spasokukotsky has been the head of the faculty surgical clinic of the 2nd Moscow Medical Institute and surgical sector of the Central Institute of Blood transfusion since 1926 until his last days of life. He has been the main surgeon of the Kremlin Medical and Sanitary Administration since 1937. His contribution to the development of organization and popularization of blood transfusion is invaluable. The developed methods of blood conservation and transportation were successfully used during the Great Patriotic War. They allowed to save hundreds of thousands of human lives.

His well-deserved awards such as Honored Worker of Science of the RSFSR (1934), Recipient of an Order of Lenin (1939), Order of the Red Banner of Labor (1943), and Winner of the Stalin Prize for Surgery and Work Entitled Activinomycosis of the Lungs (1942) were testimony of the highest mastership, service to the Motherland and its people. In 1942, S. Spasokukotsky was elected Academician of the Academy of Sciences of the USSR. He died in 1943. However, hundreds of saved patients and a large scientific school that continued developing his ideas (Bakulev AN, Berezov EL, Busalov AA, Bogoslovsky VR, Gerasimov NV, Golubev NV, Braitsev VYa, Vinograd-Finel FR, Galpern YaO, Grozdov DM, Gulyaev AV, Zhmur VA, Zaitsev GP, Kazansky VI, Kocherin IG) [10] were his legacy.

In 1948, an editorial board consisting of Bakulev AN, Busalov AA, And Kochergyn IE produced a two-volume edition of essay collection entitled 'The Essays of Academician S. Spasokukotsky' embracing the most essential scientific papers of his. The edition occupies a worthy place at the museum exhibit of the Yaroslavl State Medical University, whereas well-worn pages and completely filled in forms show that the volumes are still popular among surgeons.

References

1. Gosudarstvennyy arkhiv Yaroslavskoy oblasti (GAYAO). F. 557. Op. 1. D. 46. L. 2. Russian.
2. Popovich PP. Vrach, uchenyy, pedagog. Za meditsinskiye kadry. 1977. 6 yanvarya. Russian.
3. Stochik AM, Pal'tsev MA, Zatravkin SN. Razrabotka i vnedreniye etapnosti klinicheskogo prepodavaniya v Moskovskom universitete. M.: Shiko. 2002; 148–149. Russian.
4. Spasokukotskaya MG. Zhizn' i deyatel'nost' S. I. Spasokukotskogo. 1870–1943. M.: Medgiz. 1960; 19. Russian.
5. Deyateli meditsinskoy nauki i zdravookhraneniya — sotrudniki i pitomtsy Moskovskoy meditsinskoy akademii im. IM Sechenova. Biograficheskiy slovar'. 175–2008 gg. pod red. MA Pal'tseva, AM Stochika, SN Zatravkina. 1-ye izd. M.: Shiko. 2008; 315. Russian.
6. Spasokukotskiy SI. …Slovo v zashchitu kostnoy plastiki pri amputatsiyakh. Vrach. 1900; 6; Spasokukotskiy SI Gnoynoye vospaleniye kolennogo sustava pri raneniyakh i yego khirurgicheskoye lecheniye. Russkiy khirurgicheskiy arkhiv. 1902. Kn. 5. Russian.
7. Lyudi russkoy nauki. Ocherki o vydayushchikhsya deyatelyakh yestestvoznaniya i tekhniki pod red. IV Kuznetsova. M.: Fizmatgiz. 1963; 654. Russian.
8. Spasokukotskaya MG. Ukaz. soch.s. 83. Russian.
9. Demchenko T. Derzaniye. Neprotorennymi dorogami. Sbornik ocherkov. Saratov: Privolzhskoye knizhnoye izdatel'stvo. 1981; 42. Russian.
10. Korotkikh RV. SI Spasokukotskiy i yego shkola. M.: Meditsina. 1983; 123–127. Russian.

Литература

1. Государственный архив Ярославской области (ГАЯО). Ф. 557. Оп. 1. Д. 46. Л. 2.
2. Попович П. П. Врач, ученый, педагог. За медицинские кадры. 1977. 6 января.
3. Сточик А. М., Пальцев М. А., Затравкин С. Н. Разработка и внедрение этапности клинического преподавания в Московском университете. М.: Шико. 2002; 148–149.
4. Спасокукоцкая М. Г. Жизнь и деятельность С. И. Спасокукоцкого. 1870–1943. М.: Медгиз. 1960; 19.
5. Деятели медицинской науки и здравоохранения — сотрудники и питомцы Московской медицинской академии им. И. М. Сеченова. Биографический словарь. 175–2008 гг. под ред. М. А. Пальцева, А. М. Сточика, С. Н. Затравкина. 1-е изд. М.: Шико. 2008; 315.
6. Спасокукоцкий С. И. …Слово в защиту костной пластики при ампутациях. Врач. 1900; 6; Спасокукоцкий С. И. Гнойное воспаление коленного сустава при ранениях и его хирургическое лечение. Русский хирургический архив. 1902. Кн. 5.
7. Люди русской науки. Очерки о выдающихся деятелях естествознания и техники под ред. И. В. Кузнецова. М.: Физматгиз. 1963; 654.
8. Спасокукоцкая М. Г. Указ. соч.с. 83.
9. Демченко Т. Дерзание. Непроторенными дорогами. Сборник очерков. Саратов: Приволжское книжное издательство. 1981; 42.
10. Коротких Р. В. С. И. Спасокукоцкий и его школа. М.: Медицина. 1983; 123–127.

ETHICAL ISSUES IN IMPLEMENTING ARTIFICIAL INTELLIGENCE IN HEALTHCARE

Koshechkin KA[1] ✉, Khokhlov AL[2]

[1] First Moscow State Medical University named after I. M. Sechenov, Moscow, Russia

[2] Yaroslavl State Medical University, Yaroslavl, Russia

The integration of artificial intelligence (AI) in healthcare presents unprecedented opportunities for improving patient care and outcomes, yet it also brings forth a myriad of ethical dilemmas that demand careful consideration. This article examines the ethical challenges posed by AI in healthcare, ranging from concerns about algorithmic bias and patient privacy to issues of transparency, accountability, and professional autonomy. Through a comprehensive analysis of relevant literature, case studies, and regulatory considerations, the study explores the multifaceted ethical implications of AI technologies in clinical practice. Key findings underscore the importance of promoting transparency and accountability in AI algorithm development and deployment, as well as the need for robust regulatory oversight and ethical guidance to ensure patient rights and safety. Despite the complexities and challenges, AI offers immense potential to enhance patient care and healthcare efficiency when navigated responsibly and ethically. By prioritizing ethical principles and collaborative efforts, stakeholders can harness the transformative power of AI while upholding the highest standards of ethical healthcare practice.

Keywords: Artificial Intelligence (AI), Healthcare Ethics, Patient Privacy, Ethics of Artificial Intelligence

✉ **Correspondence should be addressed**: Konstantin A. Koshechkin
Nikitsky Boulevard, 13/1, of. 504, Moscow, 119991, Russia; koshechkin_k_a@staff.sechenov.ru

Received: 16.02.2024 **Accepted:** 02.03.2024 **Published online:** 31.03.2024

DOI: 10.24075/medet.2024.006

ЭТИЧЕСКИЕ ПРОБЛЕМЫ ВНЕДРЕНИЯ ИСКУССТВЕННОГО ИНТЕЛЛЕКТА В ЗДРАВООХРАНЕНИИ

К. А. Кошечкин[1] ✉, А. Л. Хохлов[2]

[1] Первый Московский государственный медицинский университет имени И. М. Сеченова, Москва, Россия

[2] Ярославский государственный медицинский университет, Ярославль, Россия

Интеграция искусственного интеллекта (ИИ) в здравоохранение открывает новые возможности для улучшения ухода за пациентами и улучшения результатов терапии, но при этом порождает множество этических дилемм, которые требуют тщательного рассмотрения. В этой статье рассматриваются этические проблемы, возникающие при использовании ИИ в здравоохранении: от опасений по поводу алгоритмической предвзятости и конфиденциальности пациентов до вопросов прозрачности, подотчетности и профессиональной автономии. Благодаря всестороннему анализу соответствующей литературы, тематических исследований и нормативных документов исследование описывает многогранные этические последствия применения технологий ИИ в клинической практике. Ключевые результаты подчеркивают важность повышения прозрачности работы алгоритмов и объяснимости результатов при создании и внедрении систем на основе ИИ, а также необходимость надежного нормативного надзора и этических рекомендаций для обеспечения прав и безопасности пациентов. Пациенты должны иметь четкое представление о том, как ИИ используется в их лечении, и иметь возможность дать информированное согласие на его применение. Несмотря на сложности и проблемы, ИИ несет в себе потенциал для улучшения эффективности системы здравоохранения при условии ответственного и этического подхода. Отдавая приоритет этическим принципам и совместным усилиям, заинтересованные стороны могут использовать преобразующую силу ИИ, одновременно поддерживая самые высокие стандарты этической практики здравоохранения.

Ключевые слова: искусственный интеллект (ИИ), этика в здравоохранении, конфиденциальность пациентов, этика искусственного интеллекта

✉ **Для корреспонденции:** Константин Александрович Кошечкин
Никитский бульвар, д. 13/1, оф. 504, г. Москва, 11999, Россия; koshechkin_k_a@staff.sechenov.ru

Статья поступила: 16.02.2024 **Статья принята к печати:** 02.03.2024 **Опубликована онлайн:** 31.03.2024

DOI: 10.24075/medet.2024.006

Integration of artificial intelligence (AI) in healthcare is rapidly expanding making a revolution in various aspects of the industry. AI includes a number of technologies such as machine learning, natural language processing [1] and robotics, which are used to improve medical aid and treatment outcomes of patients [2] and optimize effectiveness of the organizational activity.

In medical diagnostics, AI-based systems can analyze medical images such as X-rays, magnetic resonance imaging and computed tomography with high accuracy and allow doctors to perform early detection and diagnostics of diseases. These systems can find subtle regularities and abnormalities, which can be missed by a human observer. It can eventually result in a faster and more exact diagnostics [3]. These systems also allow to decrease the load on doctors during massive screenings by separating medical images with no pathology from studies that require special attention of specialists.

Moreover, AI transforms treatment planning and personalized medicine [4] by analyzing large patient-related data sets including genetic profiles, case histories and treatment outcomes. Machine learning algorithms can find correlations and regularities related to the data. This helps to predict patient's reactions to different methods of treatment and adapt interventions respectively [5].

Apart from diagnostics and treatment, AI is used to monitor patients and provide remote care. AI-equipped wearables can continuously collect and analyze physiological data, which allows to detect health-related data at an early stage and take prevention measures. AI-based telemedicine platforms make consultations and remote monitoring easier by improving access to medical services, especially in the areas with low service level [6, 7].

Moreover, AI-based systems of healthcare management optimize administrative tasks, distribute resources better and

improve the processes of decision taking. The systems can analyze large data sets taken from e-cards, billing systems and administrative data bases to find tendencies, inefficiencies and room for improvement [8, 9].

Though AI integration into healthcare has great prospects, it also raises essential ethical, legal and social issues. Ensuring confidentiality, transparency of algorithms and responsibility for treatment of patients during development and implementation of AI-based technologies is important during implementation of the entire potential of these innovations while preserving trust and integrity of healthcare systems [10–12].

In a fast-evolving employment landscape of healthcare technologies, AI opens up huge perspectives for a revolution in care, diagnostics, treatment and research. However, potential advantages are accompanied by essential ethical considerations which should be properly taken into account to ensure reliable development and implementation of AI technologies.

The basic ethical imperative in healthcare includes the priority in patient's welfare and safety. AI technologies can improve treatment outcome of patients. They also create new risks such as algorithmic bias, violated confidentiality of data and mistakes while taking decisions. When the AI systems are developed and implemented, we need to take into account some ethical considerations to reduce harm and improve benefit for patients [13].

AI can improve access to healthcare expanding coverage of medical knowledge and resources. However, there exists a risk that AI-based decisions can make the existing disproportions worse if they are not thoughtfully applied. The ethical frames should include the issues of inclusivity and accessibility. Then it will be warranted that AI is useful for all patients irrespective of their social and economic status, geographical position and other factors [7].

AI ethical development requires algorithms to work properly and explanation of results used while creating and implementing AI-based systems during the entire technology life cycle. It includes transparency of taking algorithmic decisions, sources and use of data, and the possibility to comprehend and dispute AI-based recommendations. Moreover, clear accountability mechanisms are required to eliminate mistakes, prejudices and unforeseen consequences, which can occur as a result of AI deployment [14].

Autonomy and informed consent: respect for a patient's autonomy and right to take reasonable decisions about medical intervention belong to basic ethical principles. As AI technologies are more integrated into the clinical practice, patients should be clearly aware of how AI is used in treatment and be able to provide informed consent. This includes transparency of limitations and uncertainties of AI systems and involvement of medical workers in decision taking.

Professional integrity and trust: medical workers should act for the benefit of patient's interests and apply ethical standards to practice. AI integration should add to experience and judgements of suppliers of medical services but not replace them. Ethical principles should support an exact use of AI as a tool to improve the process of taking clinical decisions, increase effectiveness of working processes and improve outcomes of treatment by preserving trust and integrity of relations between a patient and a supplier of medical services.

While AI continues to penetrate into various aspects of healthcare (from diagnostics and treatment to administrative tasks and interaction with patients), it gives birth to many ethical considerations that need to be examined properly. A landscape of ethical issues, which are associated with AI in healthcare, is described in the article. Ethical consequences of using AI in healthcare have been studied: from dangers related to confidentiality of patents and safety of data to potential algorithmic prejudice and discrimination, issues about accountability of AI systems while taking clinical decisions, risk of undermining confidence between patients and doctors in case of automated interventions and ethical responsibility of medical workers [12].

MATERIALS AND METHODS

The existing literature related to AI integration into healthcare has been reviewed. It included scientific journals, materials of conferences, other available literature sources and respective reports of regulating authorities and professional companies. Search inquiries included combinations of some key words such as 'artificial intellect', 'machine learning', 'healthcare', 'ethics', 'transparency', 'accountability' and 'regulation'.

Certain cases and incidents when AI technologies resulted in ethical dilemmas in medical institutions have been found and analyzed. Criteria of case selection included relevance, variety of ethical issues and availability of similar data. Thematic reviews were taken from the published literature, news articles and recorded legal or regulatory cases.

Regulatory and ethical frameworks dealing with development and implementation of AI algorithms in healthcare have been reviewed. They include respective laws, standard regulations and ethical principles issued by respective state bodies, professional communities and international organizations. Key regulating documents include materials published by the Federal Food and Drug Administration of the USA (FDA) [15], European Union General Regulation on Data Protection (GDPR) [16], Medical Ethics Code of American Medical Association (AMA) and IEEE Global Initiative related to Ethical Aspects of Artificial Intelligence and Autonomous Systems [17].

Data collection included collection of data from various sources including scientific articles, news, political documents and legal precedents. The data were analyzed using qualitative methods including thematic analysis, finding common topics, ethical dilemmas and regulatory issues associated with AI integration in healthcare. Thematic studies were analyzed with a case study to examine certain ethical issues, involved parties concerned and results for every case.

Results of literature review, thematic studies and statutory and regulatory analysis were generalized to present an extensive review of AI-related ethical problems in healthcare. Ethical consequences, regulation gaps and strategies contributing to transparency and accountability were discussed in the light of research results and existing literature. Recommendations for politicians, suppliers of medical services and other interested parties were suggested on the basis of the results and research analysis.

Limitations of the study such as potential systematic mistakes in the selected literature and thematic studies were accepted. Efforts were taken to mitigate bias by inclusion of various points of view and sources of information. The study was mainly concentrated on ethical aspects associated with AI in healthcare without dealing with technical aspects of AI algorithms or the problem of implementation. Materials and methods used during this research were aimed at the proper and systematical analysis of ethical issues associated with AI in healthcare and at the development of strategies that help to solve the problems in practice.

RESULTS AND DISCUSSION

Lack of transparency and accountability

Lack of transparency and accountability in AI algorithms belongs to one of the most pressing ethical issues associated with AI integration in healthcare. As AI systems become

more complex and autonomous, the comprehension of how the algorithms take the decisions becomes crucial to ensure justice, equality and safety of patients.

AI algorithms commonly function as 'black boxes'. It means that their processes of decision taking are not transparent and complex for interpretation or proper examination. Lack of transparency creates significant problems both for suppliers of medical services and regulatory bodies and patients as it prevents from assessing reliability, exactness and potential prejudice which are typical of AI-based recommendations. Concerns about algorithmic prejudice, discrimination and unjust attitude are obvious in healthcare where solutions have serious consequences for treatment outcomes and welfare of patients. AI systems trained based on biased and incomplete data can eternalize and exacerbate the existing inequality in rendering medical aid for certain groups of population. Moreover, non-transparency of AI algorithms makes it difficult to detect and eliminate prejudice and discrimination cases. In the lack of transparency, it is difficult to establish whether AI-based recommendations influence such factors as nationality, gender, social and economic status or other sensitive characteristics [18].

Lack of accountability further exacerbates the ethical issues as it is commonly not clear who is responsible for the actions and solutions of AI-systems in medical institutions. When AI algorithms result in erroneous or harmful results, determination of liability can be associated with legal and ethical difficulties.

To solve the issues, it is extremely important to give priority to transparency and accountability while developing and implementing AI algorithms in healthcare. This promotes open access to algorithmic methodologies and sources of data, creating conditions for independent audit and validation of AI systems, development of clear mechanisms of asking for medical aid and recovery of damage in case of algorithmic errors or causing harm.

The issues of confidentiality and safety of patient's data

In the era of digital healthcare, when large patient-related data sets are generated, collected and analyzed, concerns about data confidentiality and safety become more and more serious. AI integration in healthcare exacerbates the problems because AI systems significantly depend on access to large data sets to train algorithms and take reasonable decisions. However, collection, storage and exchange of confidential medical data are connected with significant ethical issues, which should be decided to protect confidentiality of patients and data safety.

One of the main problems includes the possibility of an unauthorized access to medical data whether as a result of cyber-attacks, data leakage or unauthorized disclosure. Unauthorized access to confidential medical data does not only threaten personal privacy but also poses risks to safety. Patients can expect that their medical data will be handled in a responsible way and that violation of trust can have remote consequences both for people and for medical organizations.

Moreover, distribution of interrelated healthcare systems and data exchange between platforms and institutions raise additional concerns about functional compatibility and data control. Patients can be informed not well enough and have poor control over how their data are collected, transferred and used. This makes them feel that they are vulnerable and that they lost their autonomy. Moreover, aggregation of separated data sets to educate AI can unintentionally disclose confidential information or promote repeated identification of people. This creates risks for inviolability of private life and confidentiality of patients [19].

Apart from external threats, internal risks (improper use of data, unauthorized access of medical personnel and unauthorized data leakage) are worth of attention, too. Suppliers of medical services and organizations should implement reliable systems of data management, means of access control, deciphering mechanisms and audit protocols. Then they will reduce these risks and ensure safe treatment of medical data of patients during the entire life cycle. Ethical considerations associated with confidentiality of patients and safety of data are beyond compliance with regulatory requirements and cover wider principles of respecting autonomy, confidentiality and confidence. Patients should be able to take reasonable decisions related to collection, use and exchange of medical data. Suppliers of medical services should follow the highest standards of safety and confidentiality of data [17].

As soon as electronic medical cards (EMC) and portable devices of health monitoring appeared, huge sets of confidential data are collected on a regular basis. They include personal identifiers, case history, diagnostic test results, treatment plans, etc. [19].

Collection of the comprehensive body of data raises concerns about unauthorized access, unauthorized use or operation, especially when the data are not properly anonymized.

Data storage and safety

Storage of confidential medical data in digital format creates vulnerabilities for cyber-attacks, data leakage and unauthorized access. Healthcare institutions should invest into reliable measures of data safety including encrypting, access control, firewalls, and intrusion detection systems to protect patient's data from intruders. Exchange of health-related data among suppliers of medical services, researchers, insurance companies and other organizations is essential for treatment coordination, conduction of studies and facilitating the exchange of data. However, it poses risks to personal privacy and confidentiality of patients. Inadequate data exchange protocols, weak mechanisms of authentication and insufficient measures of data protection can result in unauthorized data disclosure, breach in confidentiality and potential harm for patients.

Healthcare organizations should be guided by regulatory requirements concerning collection, storage and exchange of confidential medical information. They include such laws as Health Insurance Portability and Accountability Act (HIPAA) in the USA, General Data Protection Regulation (GDPR) in the EU, and Federal Law 'On Personal Data' as of 27.07.2006 № 152-FZ describing strict safety measures to protect confidentiality of patients and data safety [16, 20].

Non-compliance with these data can result in serious fines, reputation damage and loss of patient trust. Ethical considerations go beyond simple compliance with regulatory acts and cover wider principles of harmlessness, fairness and respect for patients' rights.

Potential erosion of confidence between a patient and a doctor

In medical institutions, patient-doctor relationship is characterized by confidence, empathy and joint decision taking. Nevertheless, growing AI integration in healthcare introduces a new dynamic that can undermine the confidence and worsen attitudes between a patient and supplier of medical services. Patients often attach great importance to human communication, which they share with medical workers.

Introduction of decision process taking and AI-based automatization can be perceived as replacement of human interaction with depersonalized technologies leading to the feelings of alienation, division and distrust.

The patients can be scared that AI systems lack empathy, comprehension and intuition, which is typical of medical workers. The fact reduced the quality of medical aid and experience of patients. Patients can feel uncomfortable because they trust their medical solutions to AI systems. The systems do not totally comprehend what raises concerns about transparency, accountability and possibility of errors or prejudice.

Patients also value autonomy and ability to actively participate in taking health-related decisions. Growing dependence on taking decisions based on AI and automatization systems can weaken patient's feeling of control over treatment and make them feel disenfranchised and marginalized. Patients can worry that AI systems can prioritize effectiveness and efficiency but not individual preferences. This will result in solutions that won't be in line with personal goals or preferences. Wide implementation of AI technologies in healthcare can question the authority and experience of doctors especially if AI systems are perceived as more perfect or more exact as compared to human doctors [21].

Patients can doubt the value of a doctor's contribution and search for confirmation or second opinion from several sources including AI based systems. This can undermine the authority and confidence in suppliers of medical services. Support of autonomy, confidentiality and confidence of a patient requires suppliers of medical services to comply with a delicate balance between the use of AI technologies and preservation of basic human elements in the relations between patients and supplier of medical services.

Legal and regulatory uncertainty associated with responsibility in case of AI associated errors or harming patients

AI integration in healthcare creates new legal and regulatory problems associated with responsibility in those cases when AI systems promote mistakes or harm patients. When AI technologies are becoming more autonomous and common in the clinical setting, clarifying the legal framework governing accountability is essential to protect patient's rights, ensure justice, and build confidence in AI-based healthcare [22].

AI algorithms commonly act as complex and dynamic systems which are developed owning to education and adaptation. Complex nature of these algorithms may hamper connection of errors or unfavorable results with certain actions or decisions. It becomes more difficult to define responsibility.

Traditional legal basis can hardly take into account peculiarities of AI technologies. This will result in uncertainty about distribution of responsibility between developers of software components, manufacturers of AI-based equipment, suppliers of medical services and other involved parties. Definition of who is responsible for errors or harm resulted from the use of AI is a doubtful issue, which does not have a clear precedent or guideline in many jurisdictions. Questions arise as to where the developer or manufacturer of the AI system, supplier of medical services who is using the technology or all of them can be responsible.

The level of human involvement and control in the process of AI-based decision taken makes distribution of liability even more complicated. Suppliers of medical services can assert that they were acting in accordance with the established protocols and recommendations, whereas developers can assert that their algorithms were used properly and in an honest manner. Establishing standards of rendering medical aid and due diligence during development, implementation and use of AI technologies in healthcare is essential to reduce risks and ensure safety of patients. However, defining the standards in the context of rapidly developing AI systems is a serious issue [22].

Suppliers of medical services can stick to various standards of rendering medical aid depending on the level of their acquaintance with AI technologies, education and access to resources. Similarly, developers and manufacturers are expected to comply with the best industrial practices and quality measures to minimize the risk of mistakes or harm resulting from the use of AI.

Legal and ethical consequences: legal and regulatory uncertainty associated with the responsibility occurring in case of errors or harm associated with AI. It has deep ethical consequences for safety, justice and accountability of patients. Patients have a right to demand indemnification and compensation for harm inflicted by AI technologies. Nevertheless, lack of clear legal standards can prevent from asking for help. Removal of these uncertainties requires cooperation between legal experts, suppliers of medical services, AI developers and those who defend the rights of patients to develop complex mechanisms that balance innovations and protection of patients. They also support the principles of ethical medical practice.

AI influence on medical workers, including their change in roles, obligations and professional autonomy

Integration of AI in healthcare changes roles, obligations and professional autonomy of medical workers creating both possibilities and problems while helping patients. AI technologies expand and transform the roles of medical workers in different areas including diagnostics, treatment planning, data analysis and administrative tasks.

Suppliers of medical services are increasingly cooperating with AI systems by using their abilities to improve the process of taking clinical decisions, increase effectiveness of working processes and optimize distribution of resources.

For instance, radiologists can use AI algorithms to interpret medical images, primary care physicians can use the tools that support taking clinical AI-based decisions to provide treatment recommendations. Nurses can rely upon

AI-based chat bots to educate and support patients. AI can optimize the working processes in healthcare, reduce the administrative load and increase exactness and validity of clinical tasks. By automatizing routine tasks and using data-based analytics, medical workers can concentrate on more complicated and useful types of activity. AI based predictive analytics can detect patients with high risk of adverse events. They allow suppliers of medical services to intervene into and personalize treatment plans based on individual characteristics and requirements of patients.

Though AI technologies offer significant advantages as far as effectiveness and accuracy go, they also raise concerns about erosion of professional autonomy and decision-making power among medical workers. Suppliers of medical services may fear that AI systems will take control, especially when the algorithms act as 'black boxes' with non-transparent processes of decision taking. Support of professional autonomy requires to comply with a delicate balance between using AI as a tool to improve clinical practice and preserve experience, judgements and discretion of medical workers.

Examples. Case or incidence studies when AI technologies caused ethical dilemmas in medical institutions.

Algorithmic bias in diagnostic tools

Case: according to the study, the AI-based diagnostic tool used in dermatology shows the racial bias as it was less accurate while detecting skin diseases among patients with a darker skin color as compared with fair-skinned patients.

Ethical dilemma: algorithmic bias has raised concerns about unequal access to medical aid and its outcomes as patients from racial and ethnic minority groups cannot obtain sufficient help due to inaccuracies in AI-based diagnostic tools. To eliminate the bias, transparent and inclusive data collection, algorithmic audit and constant assessment are in need to ensure just provision of medical services [23, 24].

Incorrect treatment recommendations

Case: AI-based clinical decision support system recommends a high-risk surgical procedure based on incomplete or inaccurate data. This leads to unnecessary complications and unfavorable outcomes.

Ethical dilemma: the incident stressed that it is important to ensure accuracy, reliability and clinical validity of AI-based recommendations. Suppliers of medical services came across ethical dilemmas on whether the AI-based system should be trusted or it is better to use own experience and judgement to decline potentially erroneous offers. To find the balance between advantages of supporting AI-based decisions and need in clinical discretion and accountability, clear regulatory principles, education and surveillance mechanisms are required [6].

Breach of confidentiality in predictive analytics

Case: a medical organization introduced AI-based predicative analytics to detect patients with a high risk of chronic diseases. However, a data breach was experienced. It compromised confidentiality of medical information and exposed patients to privacy risks.

Ethical dilemma: the incident raised concerns for the compromise between accurate prediction and confidentiality of patients. Suppliers of medical services came across ethical dilemmas in relation to proper use of AI-based predictive analytics to improve health outcomes while preserving confidentiality and autonomy of patients. Enhancing data security, obtaining informed consent and introducing transparent structures of data management are essential to solve the ethical issues [25].

Autonomous decision taking in intensive care units

Case: the AI controlled autonomous robotic surgical system broke down during a complex surgical procedure harming a patient. The system failure was associated with technical failures, insufficient data for education and inadequate control by a human being.

Ethical dilemma: the incident raised issues about the proper level of AI-based system autonomy in healthcare and responsibility of suppliers of medical services for safety of patients. To find a balance between the potential advantages of AI-based automatization and need in human surveillance, intervention and accountability, a reliable assessment of risks, testing protocols and surveillance by the regulatory bodies are required [26].

Strategies of transparencies and accountability in A algorithms

Designing the AI algorithms with an open-source code allows to obtain better transparency by making the source code accessible to the public. This allows researchers, developers and medical workers properly examine algorithms, comprehend their internal working and detect potential prejudices or disadvantages. Development with an open-source code promotes cooperation, expert assessment and exchange of knowledge. This results in more reliable and responsible AI-based decisions. Promoting transparency and inclusiveness, initiatives with an open-source code can increase public confidence in AI technologies.

Audit of algorithms includes a systematic assessment of AI algorithms to assess their productivity, reliability, justice, and ethical consequences. Audit can also include examination of training data, assessment of model accuracy, testing for bias or discrimination, assessment of how algorithmic decisions influence various involved parties. Independent audit carried out by third companies or regulating authorities can provide objective assessment of AI algorithms by helping to detect and reduce potential risks and ensuring accountability of developers and users.

Development of XAI or Explainable AI makes it possible for AI to submit transparent explanations to its decisions and prognoses. XAI methods are aimed to dispel the myths about complex AI models and make it easier for people to understand how they speculate. By improving interpretability and explanation, XAI promotes confidence, accountability and taking AI-based decisions at medical institutions. Patients, suppliers of medical services and regulating bodies can better understand and properly examine AI recommendations. Then they will be able to take more reasonable decisions and improve treatment outcomes [24].

To make AI algorithms more transparent and accountable, transparent methods of dealing with data and reliable systems of data management are required. They include recording data sources, methods of data collection, methods of preliminary data treatment and policies of data use. Transparent data management methods allow involved parties to assess quality, relevance and representativity of training data used to develop AI algorithms. Implementing measures to manage data (anonymization of data, data minimization and data access control) helps to protect confidentiality of patients and reduce risks of unauthorized or improper use of data.

Regulatory surveillance and standards

Establishing regulating surveillance and standards for AI algorithms in healthcare is essential for transparency, accountability and compliance of ethical principles and legislation requirements. Regulating authorities can develop guidelines, regulations and certification processes to regulate development, deployment and use of AI technologies in healthcare [17]. For instance, over 10 standards for AI in healthcare were developed in the Russian Federation. Standards (GOST R 59921.8–2022 and GOST R 59921.9–2022) establishing general requirements to AI systems in medicine and systems of quality management entered into force in Russia on January 1, 2023.

Surveillance on the part of regulating bodies makes us sure that AI algorithms correspond to minimum standards of quality, safety and manufacture by building trust between patients, suppliers of medical services and politicians. Compliance with regulatory requirements allows to reduce risks, ensure safety of patients and comply with ethical standards in healthcare on the basis of AI.

CONCLUSION

AI integration in healthcare opens great prospects in transformation of care for patients, increased accuracy of diagnostics and rendering improved medical aid. But as soon as AI technologies are becoming more common in clinical practice, they also give rise to complex ethical issues, which should be solved as soon as possible to ensure reliable and justifiable

rendering of medical aid. Transparency and accountability are especially important during development and implementation of AI algorithms. Such strategies as development with an open-source code, audit of algorithms and explainable AI can increase trust, reliability and ethics of taking AI-based solutions in healthcare. Regulating bodies, legislative bodies, suppliers of medical services and other involved parties play a key role in the development of guidelines, standards and frames regulating ethical use of AI in healthcare. In spite of problems and complex issues related to AI integration in healthcare, AI technologies produce a positive effect on treatment outcomes of patients, better healthcare effectiveness and stimulation of innovations. When the involved parties stick to ethical principles, ensure transparency and accountability and pay primary attention to welfare of patients, they can utilize the modifying AI potential and support the highest standards of ethical medical practice. Solution of ethical issues associated with AI in healthcare requires coordinated efforts of all involved parties to achieve the balance between innovations and ethical considerations. By solving the issues jointly and in a responsible way, we can warrant that AI technologies will ensure healthcare development preserving trust, dignity and rights both of patients and medical workers.

Reference

1. Yang X, et al. A large language model for electronic health records. npj Digit. Med. Nature Publishing Group. 2022; 5(1): 1–9.
2. Koshechkin KA, Polikarpov AV, Radzievsky GP. Digital technologies to improve effectiveness of pharmacotherapy. Procedia Computer Science. 2018; 126. Russian.
3. Medicine of the Future: EMC Introduces Breakthrough uMEDp Remote Diagnostics Technology in Russia. Available from URL: https://umedp.ru/press_releases/medicine_of_the_future_emc_introduces_in_russia_breakthrough_technology_for_remote_diagnostics.html (accessed: 30.05.2022). Russian.
4. Schork NJ. Artificial Intelligence and Personalized Medicine. Cancer Treatment and Research. Springer International Publishing. 2019; 178: 265–283.
5. Kormiltsyn A, Ljalik J. Multi Agent-Supported Dynamical Integration of Electronic with Personal Health Records on Blockchains for Ad-hoc Healthcare Quality Improvements. SmartHealthCareToday. 2018.
6. Lebedev G, et al. Building a telemedicine system for monitoring the health status and supporting the social adaptation of children with autism spectrum disorders. Smart Innovation, Systems and Technologies. Springer Science and Business Media Deutschland Gmb H. 2019; 143:287–294.
7. Donnelly D-L, Donnelly D. First Do No Harm: Legal Principles Regulating the Future of Artificial Intelligence in Health Care in South Africa. Potchefstroom Electron. Law J. North West University. 2022; 25(1): 1–43.
8. Amisha, et al. Overview of artificial intelligence in medicine. J. Fam. Med. Prim. care. Medknow. 2019; 8 (7): 2328–2331.
9. Tsyndymeyev A, Koshechkin K, Lebedev G. Scientific approaches to the digitalization of drugs assortment monitoring using artificial neural networks. Smart Innovation, Systems and Technologies. 2020; 193. Russian.
10. Ota N, et al. A Concept for a Japanese Regulatory Framework for Emerging Medical Devices with Frequently Modified Behavior. Clin. Transl. Sci. Wiley-Blackwell. 2020;13(5):877.
11. De Araujo D, et al. The regulation of artificial intelligence for health in Brazil begins with the General Personal Data Protection Law 2 AI regulation for health in Brazil begins with the LGPD Dourado DA e Aith FMA.
12. Wang C, et al. Privacy Protection in Using Artificial Intelligence for Healthcare: Chinese Regulation in Comparative Perspective. Healthc. 2022; 10: 1878. Multidisciplinary Digital Publishing Institute. 2022; 10(10):1878.
13. Bak M, et al. You Can't Have AI Both Ways: Balancing Health Data Privacy and Access Fairly. Front. Genet. Frontiers Media S. A. 2022; 13: 1490.
14. Sniecinski I, Seghatchian J. Artificial intelligence: A joint narrative on potential use in pediatric stem and immune cell therapies and regenerative medicine. Transfus. Apher. Sci. Elsevier Ltd. 2018; 57(3): 422–424.
15. Cder Cber F. Using Artificial Intelligence & Machine Learning in the Development of Drug and Biological Products.
16. GDPR text in Russian with comments and links | GDPR-Text.com. Available from URL: https://gdpr-text.com/ru/ (accessed: 23.01.2023).
17. IEEE Global Initiative on Ethics in Artificial Intelligence and Autonomous Systems Available from URL: https://standards.ieee.org/wp-content/uploads/import/documents/other/ead_executive_summary_russian_v1.pdf (accessed: 14.02.2024).
18. Jonathon Phillips P, et al. Four Principles of Explainable Artificial Mark A. Przybocki.
19. Siyal A.A. et al. Applications of Blockchain Technology in Medicine and Healthcare: Challenges and Future Perspectives. Cryptography. MDPI AG. 2019; 3 (1): 3.
20. Griggs K.N, et al. Healthcare Blockchain System Using Smart Contracts for Secure Automated Remote Patient Monitoring. J. Med. Syst. Springer New York LLC, 2018; 42(7):130.
21. Jarzabek G, Schucht P, Rzeczkowski L. Patient and doctor-centric health ecosystem in specialised medicine engineered on blockchain. 2017.
22. Bochenek T, et al. Systemic measures and legislative and organizational frameworks aimed at preventing or mitigating drug shortages in 28 European and Western Asian Countries. Front. Pharmacol. Frontiers Media S. A. 2018; 8. DOI: 10.3389/fphar.2017.00942
23. Efimenko M, Ignatev A, Koshechkin K. Review of medical image recognition technologies to detect melanomas using neural networks. BMC Bioinformatics. 2020; 21.
24. Pouly M, et al. Artificial intelligence in image analysis — fundamentals and new developments. Hautarzt. Springer Medizin, 2020; 71(9): 660–668.
25. Liu H, Crespo RG, Martínez OS. Enhancing Privacy and Data Security across Healthcare Applications Using Blockchain and Distributed Ledger Concepts. Healthcare. MDPI AG. 2020; 8(3): 243.
26. Da Vinci robotic surgeon accused of murdering a woman. Available from URL: https://naked-science.ru/community/929220 (accessed: 14.02.2024).

Литература

1. Yang X, et al. Большая языковая модель для электронных медицинских карт. npj Digit. Med. Nature Publishing Group. 2022; 5(1): 1–9.
2. Кошечкин К.А., Поликарпов А. В., Радзиевский Г. Цифровые технологии повышения эффективности фармакотерапии. Procedia Computer Science. 2018; 126.
3. Медицина будущего: EMC внедряет в России прорывную технологию удаленной диагностики uMEDp. Режим доступа: [Электронный ресурс] URL: https://umedp.ru/press_releases/medicine_of_the_future_emc_introduces_in_russia_breakthrough_technology_for_remote_diagnostics.html (дата обращения: 30.05.2022).
4. Шорк Н. Д. Искусственный интеллект и персонализированная медицина. Cancer Treatment and Research. Springer International Publishing. 2019; 178: 265–283.
5. Кормильцын А. В., Лялик Ю. Динамическая интеграция электронных и персональных медицинских карт на блокчейне с поддержкой нескольких агентов для ситуативного

повышения качества здравоохранения. SmartHealthCareToday. 2018.
6. Lebedev, et al. Building a telemedicine system for monitoring the health status and supporting the social adaptation of children with autism spectrum disorders. Smart Innovation, Systems and Technologies. Springer Science and Business Media Deutschland Gmb H. 2019; 143: 287–294.
7. Доннелли Д.-Л., Доннелли Д. Прежде всего, не навреди: правовые принципы, регулирующие будущее искусственного интеллекта в здравоохранении в Южной Африке. Potchefstroom Electron. Law J. North West University. 2022; 25(1): 1–43.
8. Амиша и др. Обзор искусственного интеллекта в медицине. J. Fam. Med. Prim. care. Medknow. 2019; 8(7): 2328–2331.
9. Циндымеев А., Кошечкин К., Лебедев Г. Научные подходы к цифровизации мониторинга ассортимента лекарственных средств с использованием искусственных нейронных сетей. Smart Innovation, Systems and Technologies. 2020;193.
10. Ota N, et al. Концепция японской нормативно-правовой базы для новых медицинских изделий с часто изменяемым поведением. Clin. Transl. Sci. Wiley-Blackwell. 2020; 13(5): 877.
11. De Araujo D, et al. Регулирование искусственного интеллекта в здравоохранении в Бразилии начинается с Общей защиты персональных данных. Law 2 AI regulation for health in Brazil LGPD DA e Aith FMA.
12. Ван К. и др. Защита конфиденциальности при использовании искусственного интеллекта в здравоохранении: китайское регулирование в сравнительной перспективе. Healthc. 2022;10: 1878. Multidisciplinary Digital Publishing Institute. 2022; 10 (10): 1878.
13. Bak M, et al. Вы не можете использовать ИИ в обоих направлениях: баланс между конфиденциальностью медицинских данных и справедливым доступом к ним. Front. Genet. Frontiers Media SA. 2022; 13: 1490.
14. Сниечински И., Сегачян Д. Искусственный интеллект: совместное повествование о потенциальном использовании в педиатрической терапии стволовыми и иммунными клетками и регенеративной медицине. Transfus. Apher. Sci. Elsevier Ltd. 2018; 57(3): 422–424.
15. Использование искусственного интеллекта и машинного обучения при разработке лекарственных и биологических препаратов. CDER CBER F.
16. Текст GDPR на русском с комментариями и ссылками | GDPR-Text.com. Режим доступа: [Электронный ресурс] URL: https://gdpr-text.com/ru/ (дата обращения: 23.01.2023).
17. Глобальная инициатива IEEE по этике в области искусственного интеллекта и автономных систем. Режим доступа: [Электронный ресурс] URL: https://standards.ieee.org/wp-content/uploads/import/documents/other/ead_executive_summary_russian_v1.pdf (дата обращения: 14.02.2024).
18. Jonathon Phillips P, et al. Четыре принципа объяснимого искусственного интеллекта. Mark A. Przybocki.
19. Siyal AA, et al. Применение технологии блокчейн в медицине и здравоохранении: вызовы и перспективы. Cryptography. MDPI AG. 2019; 3(1): 3.
20. Griggs KN, et al. Блокчейн-система в здравоохранении, использующая смарт-контракты для безопасного автоматизированного удаленного мониторинга пациентов. J. Med. Syst. Springer New York LLC. 2018; 42(7): 130.
21. Jarzabek G, Schucht P, Rzeczkowski L. Ориентированная на пациента и врача экосистема здравоохранения в специализированной медицине, разработанная на блокчейне. 2017.
22. Bochenek T, et al. Системные меры, законодательные и организационные рамки, направленные на предотвращение или смягчение дефицита лекарств в 28 странах Европы и Западной Азии. Front. Pharmacol. Frontiers Media S. A. 2018; 8. DOI: 10.3389/fphar.2017.00942
23. Efimenko M., Ignatev A., Koshechkin K. Review of medical image recognition technologies to detect melanomas using neural networks. BMC Bioinformatics. 2020; 21.
24. Pouly M, et al. Искусственный интеллект в анализе изображений: основы и новые разработки. Hautarzt. Springer Medizin. 2020; 71(9): 660–668.
25. Liu H., Crespo R. G., Martínez O. S. Повышение конфиденциальности и безопасности данных в приложениях здравоохранения с помощью концепций блокчейна и распределенного реестра. Healthcare. MDPI AG. 2020; 8 (3): 243.
26. Робота-хирурга Da Vinci обвинили в убийстве женщины. Режим доступа: [Электронный ресурс] URL: https://naked-science.ru/community/929220 (дата обращения: 14.02.2024).

DEVELOPMENT OF NEUROTECHNOLOGIES: ETHICAL ISSUES AND PUBLIC DISCUSSIONS

Khokhlov AL[1], Kotlovsky MYu[1,2] ✉, Pavlov AV[1], Potapov MP[1], Gabidullina LF[1], Tsybikova EB[2]

[1] Yaroslavl State Medical University, Yaroslavl, Russia

[2] Central Research Institute of Healthcare Organization and Informational Support, Moscow, Russia

At present, neurotechnologies are emerging rapidly. The scope of state and private investment in the trend, which is the investment priority, is growing steadily. Interstate, national initiatives and public-private alliances for their development are created. Meanwhile, a significant potential of neurotechnologies consists not only in treatment of a wide specter of diseases and disorders of the nervous system, but also in improvement of human nature. At the same time, uncontrolled use of these technologies can violate fundamental rights. This raises the questions associated with accessibility and potential use of neurotechnologies to improve the human nature. It can produce a deep effect both on certain people, and the entire society. Development of neurotechnologies requires a highly organized approach on the part of ethics and morality with subsequent fixation of these provisions in the legislative and regulatory acts. International, state and non-governmental organizations play a great role in this case.

Key words: neurotechnologies, ethics

✉ **Correspondence should be addressed:** Mikhail Yu. Kotlovsky
Revolutsionnaya Str., 5, Yaroslavl, 150000, Russia; m.u.kotlovskiy@mail.ru

Received: 20.03.2024 **Accepted:** 27.03.2024 **Published online:** 30.03.2024

DOI: 10.24075/medet.2024.005

РАЗВИТИЕ НЕЙРОТЕХНОЛОГИЙ: ЭТИЧЕСКИЕ ПРОБЛЕМЫ И ОБЩЕСТВЕННЫЕ ДИСКУССИИ

А. Л. Хохлов[1], М. Ю. Котловский[1,2] ✉, А. В. Павлов[1], М. П. Потапов[1], Л. Ф. Габидуллина[1], Э. Б. Цыбикова[2]

[1] Ярославский государственный медицинский университет, Ярославль, Россия

[2] Центральный научно-исследовательский институт организации и информатизации здравоохранения, Москва, Россия

В настоящее время стремительное развитие получили нейротехнологии. Неуклонно растет объем государственных и частных инвестиций в данное направление, выступающее инвестиционным приоритетом. Создаются межгосударственные, национальные инициативы и государственно-частные альянсы по их развитию. При этом демонстрируется значительный потенциал нейротехнологий не только в лечении широкого спектра заболеваний и расстройств нервной системы, но и в улучшении природы человека. В то же время бесконтрольное использование данных технологий, может нарушать его основополагающие права. Все это поднимает вопросы, связанные с доступностью и потенциалом использования нейротехнологий в целях совершенствования сущности, что может оказать глубокое воздействие как на отдельных людей, так и на общество в целом. Развитие нейротехнологий требует высокоорганизованного подхода со стороны этики и морали, с последующим закреплением данных положений в установочных нормативно-правовых актах. В этом большая роль отводится международным, государственным и общественным организациям.

Ключевые слова: нейротехнологии, этика

✉ **Для корреспонденции:** Михаил Юрьевич Котловский
ул. Революционная, д. 5, г. Ярославль, 150000, Россия; m.u.kotlovskiy@mail.ru

Статья поступила: 20.03.2024 **Статья принята к печати:** 27.03.2024 **Опубликована онлайн:** 30.03.2024

DOI: 10.24075/medet.2024.005

Today, neurotechnologies are defined as an area of technical devices and procedures used to obtain access to, monitor, examine, assess, manipulate and (or) emulate structures and functions of the neural systems of animals or people [1]. Meanwhile, neurotechnologies are at the junction of several disciplines such as chemistry, neurology, neuropsychology, informatics, biological engineering, computer science, material science and medical technologies. Neurotechnologies cover not only direct registration of human brain activity and direct influence or modification of brain activity. They also concern any device or application including services and interfaces based on AI and big data which can extract data from human brain activity or produce a modifying effect hereon.

It is obvious that the list of technologies has a significant potential in relation to a wide specter of diseases and disorders of the nervous system. Electronic chips implanted into the nervous tissues or wearable devices display serious potential in relation to diagnostics, treatment and prevention of neurological and mental disturbances and perspective of their use among children with limited capabilities [2].

For instance, a breakthrough method was developed in 2023. It allows people with traumatic damage to the spinal cord to move in a natural way. For this, a wireless digital interface (brain-spine interface) that transmits signals in real time should be used [3].

It should however be noticed that the area of using neurotechnologies goes far beyond the sphere of medicine and covers scientific research, education and even daily life of ordinary people. For instance, decisions based on the use of neurotechnologies can improve the process of education, acquisition of skills and increase concentration [4].

Today, neurotechnologies can reveal the human nature, secrets of the human biological basis and nature of social, ethical and, as a consequence, legally significant decisions produced by the human brain.

Owing to current perspectives, neurotechnologies attracted significant attention on the part of governments and private business. In modern times, they were considered from the perspectives of investment attractiveness [5].

Based on the International Brain Initiative (IBI), research financing has been steadily increasing during the last 10 years. It leads to the growth of large-scale government programmes aimed at advance in the technology of intervention in the human brain [6].

Starting from 2013, such national initiatives as brain research due to advance of innovative neurotechnologies in the USA (BRAIN) and European Union (HBP), and large national initiatives of China, Japan and South Korea were initiated in significant financial support of respective national governments [6–8]. The Canadian strategy of brain research, which initially acted as a multilateral coalition of involved parties in this area of research, is actively searching for financial state support to be transformed into the national research initiative [9]. A similar offer is also considered in case of the Australian Brain Alliance, which calls for initiation of the Australian National Initiative of Brain Research [10].

According to the approximate assessment of state investment into these technologies, over 6 billion US dollars were invested into this trend starting from 2012 (USA). State support is complemented by a steady growth of private investment into neurotechnologies. From 2010 to 2020, the scope of investment into the company data is increased from 331 bln to 7.3 bln US dollars (by 22 times). Meanwhile, the total scope of investment to neurological companies has achieved 33.2 bln US dollars by 2020 [11].

The pronounced surge of private investment reflects the growing market demand and expansion of implemented solutions based on these technologies. It is predicted that neurotechnologies will turn into a large area capable of yielding significant social and economic dividends in the nearest future. According to previously made prognosis, the scope of the market will account for over 17 bln US dollars by 2026 already [12]. Later studies have shown that the market of neurotechnological devices can be increased from 11.3 bln US dollars in 2021 to 24.2 bln US dollars in 2027. Meanwhile, the predicted aggregate annual growth rate during the considered period will constitute 14.4% [13].

Rapid development of neurotechnologies naturally raises a number of important ethical issues in many areas. Unlike other technological investments, neurotechnologies most frequently interact with the human brain and produce an effect hereon. This may entail deep consequences for the fundamental aspects of the human existence. They include mental integrity, inviolability of the person, human dignity, personal identity, freedom of thought, autonomy and personal privacy. This raises the questions associated with accessibility and potential use of neurotechnologies to improve the human nature. It can produce a deep effect both on certain people, and the entire society [1].

It should be noted that mental integrity of a human being means that the person can handle the mental condition and brain-related data so that nobody could have a right to read, distribute or change the condition and mentioned data without the person's consent [14].

The use of brain-computer interface (BCI) is an example of ethical issues associated with the mental integrity. The devices read signals from the human brain and transform them into commands for machines. It seems that the interfaces can help people with motors disturbances or paralysis [15]. If we admit that the devices can be hacked or manipulated by fraudulent third parties, this can produce an effect not only on the physical personal autonomy but will also result in the breach of psychological integrity of persons and their right to control own thoughts and actions.

The concept of psychological integrity also means that human dignity including body integrity and respect for the principle of equality is recognized. Article 1 of the Universal Declaration of Human Rights (UN, 1984) states that all people are born free and equal in relation to dignity and law [16]. They are endowed with intelligence and consciousness. Thus, the integrity of a human body including brain and mentality should be recognized, respected and protected from any forms of neurotechnological changes. Meanwhile, illegal modification or manipulation should be perceived as violated human dignity [1].

Neurotechnologies can influence the personal identity which is related to the ability of people to think and feel on their own [1]. Thus, deep simulation of the brain (DBS) is an example of neurotechnology that causes ethical problems associated both with human dignity, and personal identity. Deep brain stimulation is a surgical procedure when electrodes are implanted into certain areas of the brain to regulate abnormal impulses. They are often used to treat such conditions as Parkinson disease, dystonia and obsessive compulsory disorder [17]. However, DBS can change a human behavior in an ambivalent manner by decreasing positive personal capacities as well. For instance, human artistic creativity can suffer, too. A patient's memory about the past events can be distorted. In such cases, human dignity and personal identity that make people unique can be violated [18].

Growing capabilities launched by neurotechnology-associated developments including monitoring, tracking and manipulation with cognitive functions can prevent cognitive processes, especially in respect to freely taking decisions. It is of primary importance for the autonomy of an individual's will. This includes the human ability to produce independent actions that correspond to criteria of intentionality and awareness. They should be free from eternal effects aimed to control or determine human actions [19]. The autonomy of a will is closely interrelated with the concept of informed consent. In this respect, article 6 of the United Declaration of Bioethics and Human Rights (UDBHR) states that any preventive, diagnostic and therapeutic medical intervention, and research should be carried out based on preliminary, free, clearly expressed and informed consent of the involved person [20]. At the same time, neurotechnologies deal with additional problems associated with applicability of the informed consent principle as risks and benefits related to the use of these technologies are still to be evaluated. At the same time, respective information is currently knowingly incomplete or totally inaccessible for a patient.

Ethical issues which are connected with the autonomy of will and informed awareness can be caused, for instance, by methods of neurovisualization such as functional magnetic resonance tomography (fMRI) [21]. Neurovisualization can identify the individual thinking models and even predict human behavior. For instance, an employer can use the methods of neurovisualization to assess whether the considered applicants are suitable for employment. However, this would cause ethical issues associated with whether candidates can comprehend the consequences that can occur when brain scanning can find potential incorrect use of these data. For instance, unjust assessment of qualities that are not associated with work or disclosure of deep personal information such as susceptibility to certain mental diseases. In these cases, informed consent validity is undermined.

As neurotechnologies can record and transfer brain-related data and digital information associated with the brain activity,

they can intrude a human private life as well. The last concerns obviously violated protection of an individual from unauthorized intrusion of third persons into their mental data and from unauthorized collection of personal data.

Brain personal data, which are also known as neural data, include data associated with the brain functioning or structure. People unconsciously generate a significant amount of neural data. It means that individuals can unconsciously or unintendedly share data which they would never disclose to third persons otherwise [1].

Collection and treatment of data from a neurodevice can be used to identify certain people or brain activity especially in relation to stigmatization of neurological or mental health. These are the prerequisites of discrimination practice. It should be added that emotional reactions of consumers associated with individual preferences and risks can be traced not only within a medical sphere but also with neurotechnologies such as neurovisualization. Similar ownership of neuronal data can promote building more exact market-level predictions than possession of traditional behavioral data does [22].

It should be noted that effect of neurotechnologies on vulnerable population groups including children and adolescents deserves special attention. The category of people is more susceptible to potential adverse effects or unintentional consequences of neurotechnologies taking into account their continuing development of the nervous system and brain plasticity [23]. Admitting the fact that the school implemented the program within the frames of which students use BCI interfaces to increase their susceptibility to education can create some ethical issues. On the one hand, excessive dependability on BCI during the learning process can produce a negative effect on other cognitive skills of students including creativity or skills to solve problems independently. On the other hand, integration of neural devices and brain-computer interfaces during the critical development stages of the nervous system can hamper differences between personality traits and behavior.

Considering everything that was said above, in 2020 UN member states urged for the preparation of guidelines, which would promote the common agenda for all countries and reaction to the current and future human challenges (A/RES/75/1) [24]. They included digital technologies and potential ability to provoke disagreements in countries, diminish safety, undermine human rights and exacerbate personal inequality. In 2021, UN Secretary General read a report where neurotechnologies was presented as a boundary issue in the area of human rights. It had to be explained as far as the applicable frames and standards go to prevent harm in digital or technological space [25].

Currently, UNESCO plays a significant role in neurotechnologies by using its mandate and experience in bioethics. A report for the year of 2021 published by UNESCO presented an extensive review of ethical, legal and social consequences of using neurotechnologies and contained certain recommendations about possible ways of their implementation into practice [1]. Apart from guidelines of international discussions on this issue and discussions in the UN system, UNESCO raises community awareness and focuses on better political efforts in relation to neurotechnologies.

Report on risks and challenges associated with neurotechnologies in relation to human rights was published by UNESCO in 2022 in collaboration with the University of Milano-Bicocca and New York State University [26]. The report has shown a global landscape of neurotechnologies, presented data about the key participants, their development area and basic achievements.

The International Committee on Bioethics, which is an expert and consultative body of UNESCO, believes that the 'neurorights' cover certain human rights, which have already been admitted in national laws, international law and international documents on human rights. These rights are based on recognition of basic human rights to physical and mental integrity, integrity of private life, freedom of thoughts and free will, right to use the benefits of scientific progress, recognition of the necessity to protect and encourage these rights in relation to application of these neurotechnologies. They also include the right to take free and responsible decisions on the issues associated with the use of neurotechnologies without any discrimination, intimidation or violence.

Regulatory acts that protect mental health or neurodata as personal data have currently been taken at the state level in some countries only [26]. The constitutional reform conducted in Chile, Charter for the Responsible Development of Neurotechnology of the Government of France and Charter of Digital Rights of the Government of Spain can serve as examples [27–29]. The cases offer various approaches to regulation and protection of basic human rights in relation to neurotechnologies. Great Britain is currently examining the circumstances in which neuronal data can be considered as a special category of data within the general system of personal information [30].

CONCLUSION

It should be admitted today that ethical regulation of science and technology development is always late if it is based on a simple reaction to certain situations which are generated using the available or even widely applied technologies. Thus, it is necessary to predict the consequences of neurotechnology implementation beforehand by using the scenarios where society, science and technology of the future and the way they are going to interact are being reflected. Just like in case with all newly arising technologies, development of neurotechnologies requires a highly organized approach on the part of human ethics and morality. These provisions should be further fixed in legislative and regulatory acts.

Responsible innovations in neurotechnologies should constitute a result of science and society cooperation. While neurotechnology are developed, it is essential to take into account the perspectives, needs, concerns and experience of people who could use them. The educational work which is associated with what a neurotechnology is and which effects can be seen due to its development and application constitute the basic need of the today's society.

Progress in neurotechnologies needs an active interaction with the society. It is also important to ensure bilateral exchange of information and not just transfer of data from developers to users. Thus, we should strive to inclusivity by integrating interests and values to the process of creation and development of these neurotechnologies.

Attracting society attention is essential for building user's trust. This will promote a more exact adjustment of novel technologies to the needs of those who could use them. This will allow to avoid unreasonable expectations, which can produce a negative effect on public confidence in technologies and artificial intelligence.

References

1. UNESCO (United Nations Educational, Scientific and Cultural Organisation) International Bioethics Committee, Report of the International Bioethics Committee of UNESCO (IBC) on the Ethical Issues of Neurotechnology, SHS/BIO/IBC-28/2021/3 Rev. 2021. Available from URL: https://unesdoc.unesco.org/ark:/48223/pf0000378724.locale=en (accessed 10.03.2024).
2. Doidge N. The Brain that changes itself: Stories of personal triumph from the frontiers of brain science. Viking Press. 2007; 427 p. ISBN 978-8178241753.
3. Lorach H, Galvez A, Spagnolo V, Martel F, et al. Walking naturally after spinal cord injury using a brain–spine interface. Nature. 2023; 618(7963): 126–133. DOI: 10.1038/s41586-023-06094-5.
4. Cinel C, Valeriani D, Poli R. Neurotechnologies for human cognitive augmentation: current state of the art and future prospects. Front Hum Neurosci. 2019; 1:3. DOI: 10.3389/fnhum.2019.00013.
5. Galaj NI. Primenenie nejrotekhnologij v kommercheskoj sfere R (na primere marketinga bankovskih depozitnyh uslug): dis. kand. ekonom. nauk: 5.2.3. Sankt-Peterburgskij gos. universitet, Sankt-Peterburg. 2022; 315 s. Russian.
6. International Brain Initiative Tackling Global Issues in Neuroscience Research. 2021. Available from URL: https://www.internationalbraininitiative.org/news/tackling-global-issues-neuroscience-research (accessed 10.03.2024).
7. US National Institutes of Health Overview of the BRAIN Initiative®. 2023. Available from URL: https://www.nidcd.nih.gov/funding/brain-initiative-nidcd (accessed 10.03.2024).
8. Korea Brain Research Institute Brief summary of Korea Brain Initiative (KBRI). Available from URL: https://www.kbri.re.kr/new/pages_eng/sub/page.html?mc=3186 (accessed 10.03.2024).
9. Canadian Brain Research Strategy Establishing a Brain Research Initiative for Canada: Written Submission to the Standing Committee for Science and Research of the House of Commons of Canada. 2022. Available from URL: https://www.ourcommons.ca/Content/Committee/441/SRSR/Brief/BR11624221/br-external/CanadianBrainResearchStrategy-e.pdf (accessed 10.03.2024).
10. Australian Academy of Science (no date) Why Australia needs a brain initiative. Australian Academy of Science. Available from URL: https://www.science.org.au/supporting-science/other-initiatives/ausbrain/why-australia-needs-brain-initiative (accessed 10.03.2024).
11. NeuroTech ANALYTICS Global Neurotech Industry Investment Digest. 2021. Available from URL: http://analytics.neurotech.com/neurotech-investment-digest.pdf (accessed 10.03.2024).
12. Neurotech Reports. The Market for Neurotechnology: 2022–2026. 2018. Available from URL: https://www.neurotechreports.com/pages/execsum.html (accessed 10.03.2024).
13. BCC Research Neurotech Devices: Global Market Outlook. 2023. Available from URL: https://secure.livechatinc.com/ (accessed 10.03.2024).
14. Lavazza A. Freedom of thought and mental integrity: The moral requirements for any neural prosthesis. Frontiers in Neuroscience. 2018; 12: 82.
15. Gilbert F, Cook M, O'Brien T, Illes, J. Embodiment and estrangement: Results from a first-in-human 'intelligent BCI' trial. Science and engineering ethics. 2019; 25 (1): 83–96.
16. UN. Universal Declaration of Human Rights. New York, UN. 1948. Available from URL: https://www.un.org/en/about-us/universal-declaration-of-human-rights (accessed 10.03.2024).
17. Kringelbach ML, Jenkinson N, Owen SL, Aziz TZ. Translational principles of deep brain stimulation. Nature Reviews. Neuroscience: journal. 2007; 8(8): 623–635. DOI: 10.1038/nrn2196.
18. Zarzycki MZ, Domitrz I. Stimulation-induced side effects after deep brain stimulation — a systematic review. Acta Neuropsychiatr. 2020; 32(2): 57–64. DOI: 10.1017/neu.2019.35.
19. Beauchamp TL, Childress JF. Principles of biomedical ethics, fifth ed. New York: Oxford University Press. 2001; 454 p.
20. UNESCO. Universal Declaration on Bioethics and Human Rights. Paris: UNESCO. 2005. Available from URL: http://portal.unesco.org/en/ev.php-URL_ID=31058&URL_DO=DO_TOPIC&URL_SECTION=201.html (accessed 10.03.2024).
21. Rinck PA. Magnetic Resonance in Medicine. A Critical Introduction. The Basic Textbook of the European Magnetic Resonance Forum. 2023. Available from URL: https://www.trtf.eu/pubs/Textbook_AdvancedContrast.pdf (accessed 10.03.2024).
22. Karmarkar UR and Yoon C. Consumer neuroscience: advances in understanding consumer psychology. Current Opinion in Psychology. 2016; 10: 160–165. DOI: 10.1016/j.copsyc.2016.01.010.
23. Spear LP. Adolescent neurodevelopment. Journal of adolescent health. 2013; 52(2): 7–13.
24. UN. Declaration on the commemoration of the seventy-fifth anniversary of the United Nations, United Nations General Assembly. A/RES/75/1. 2020. Available from URL: https://unacov.uk/un75-declaration/ (accessed 10.03.2024).
25. UN. Our Common Agenda, report of the Secretary-General. 2021. Available from URL: https://web.archive.org/web/20230216065407/; https://www.un.org/en/content/common-agenda-report/ (accessed 10.03.2024).
26. UNESCO. University of Milan-Bicocca (Italy) and State University of New York — Downstate Health Sciences University. The risks and challenges of neurotechnologies for human rights. 2023. Available from URL: https://unesdoc.unesco.org/ark:/48223/pf0000384185.page=%5B8%5D (accessed 10.03.2024).
27. Zúñiga-Fajuri A, Miranda LV, Miralles DZ, Venegas RS. Neurorights in Chile: Between neuroscience and legal science. Developments in Neuroethics and Bioethics. 2021; 4: 165–179.
28. Government of France. Charter for the Responsible Development of Neurotechnologies. Ministry of Higher Education and Research. 2022. Available from URL: https://www.enseignementsup-recherche.gouv.fr/fr/charte-de-developpement-responsable-des-neurotechnologies-87964 (accessed 10.03.2024).
29. Government of Spain. Charter of Digital Rights.pdf. 2021 Available from URL: https://portal.mineco.gob.es/RecursosArticulo/mineco/ministerio/participacion_publica/audiencia/ficheros/Charter%20of%20Digital%20Rights.pdf (accessed 10.03.2024).
30. UK's Information Commissioner's Office ICO tech futures: neurotechnology: Regulatory issues. ICO. 2023. Available from URL: https://ico.org.uk/about-the-ico/research-and-reports/ico-tech-futures-neurotechnology/regulatory-issues/ (accessed 10.03.2024).

Литература

1. UNESCO (United Nations Educational, Scientific and Cultural Organisation) International Bioethics Committee, Report of the International Bioethics Committee of UNESCO (IBC) on the Ethical Issues of Neurotechnology, SHS/BIO/IBC-28/2021/3 Rev. 2021. Режим доступа: [Электронный ресурс]. URL: https://unesdoc.unesco.org/ark:/48223/pf0000378724.locale=en (дата обращения 10.03.2024).
2. Doidge N. The Brain that changes itself: Stories of personal triumph from the frontiers of brain science. Viking Press. 2007; 427 p. ISBN 978-8178241753.
3. Lorach H, Galvez A, Spagnolo V, Martel F, et al. Walking naturally after spinal cord injury using a brain–spine interface. Nature. 2023; 618(7963): 126–133. DOI: 10.1038/s41586-023-06094-5.
4. Cinel C, Valeriani D, Poli R. Neurotechnologies for human cognitive augmentation: current state of the art and future prospects. Front. Hum. Neurosci. 2019; 1:3. DOI: 10.3389/fnhum.2019.00013.
5. Галай Н. И. Применение нейротехнологий в коммерческой сфере Р (на примере маркетинга банковских депозитных услуг): дис. канд. эконом. наук: 5.2.3. Санкт-Петербургский гос. университет, Санкт-Петербург. 2022; 315 с.

6. International Brain Initiative Tackling Global Issues in Neuroscience Research. 2021. Режим доступа: [Электронный ресурс]. URL: https://www.internationalbraininitiative.org/news/tackling-global-issues-neuroscience-research (дата обращения 10.03.2024).
7. US National Institutes of Health Overview of the BRAIN Initiative®. 2023. Режим доступа: [Электронный ресурс]. URL: https://www.nidcd.nih.gov/funding/brain-initiative-nidcd (дата обращения 10.03.2024).
8. Korea Brain Research Institute Brief summary of Korea Brain Initiative (KBRI). Режим доступа: [Электронный ресурс]. URL: https://www.kbri.re.kr/new/pages_eng/sub/page.html?mc=3186 (дата обращения 10.03.2024).
9. Canadian Brain Research Strategy Establishing a Brain Research Initiative for Canada: Written Submission to the Standing Committee for Science and Research of the House of Commons of Canada. 2022. Режим доступа: [Электронный ресурс]. URL: https://www.ourcommons.ca/Content/Committee/441/SRSR/Brief/BR11624221/br-external/CanadianBrainResearchStrategy-e.pdf (дата обращения 10.03.2024).
10. Australian Academy of Science (no date) Why Australia needs a brain initiative. Australian Academy of Science. Режим доступа: [Электронный ресурс]. URL: https://www.science.org.au/supporting-science/other-initiatives/ausbrain/why-australia-needs-brain-initiative (дата обращения 10.03.2024).
11. NeuroTech ANALYTICS Global Neurotech Industry Investment Digest. 2021. Режим доступа: [Электронный ресурс]. URL: http://analytics.neurotech.com/neurotech-investment-digest.pdf (дата обращения 10.03.2024).
12. Neurotech Reports. The Market for Neurotechnology: 2022–2026. 2018. Режим доступа: [Электронный ресурс]. URL: https://www.neurotechreports.com/pages/execsum.html (дата обращения 10.03.2024).
13. BCC Research Neurotech Devices: Global Market Outlook. 2023. Режим доступа: [Электронный ресурс]. URL: https://secure.livechatinc.com/ (дата обращения 10.03.2024).
14. Lavazza, A. Freedom of thought and mental integrity: The moral requirements for any neural prosthesis. Frontiers in Neuroscience. 2018; 12: 82.
15. Gilbert F, Cook M, O'Brien T, Illes J. Embodiment and estrangement: Results from a first-in-human 'intelligent BCI' trial. Science and engineering ethics. 2019; 25 (1): 83–96.
16. UN. Universal Declaration of Human Rights. New York, UN. 1948. Режим доступа: [Электронный ресурс]. URL: https://www.un.org/en/about-us/universal-declaration-of-human-rights (дата обращения 10.03.2024).
17. Kringelbach ML, Jenkinson N, Owen SL, Aziz TZ. Translational principles of deep brain stimulation. Nature Reviews. Neuroscience: journal. 2007; 8(8): 623–635. DOI: 10.1038/nrn2196.
18. Zarzycki MZ, Domitrz I. Stimulation-induced side effects after deep brain stimulation — a systematic review. Acta Neuropsychiatr. 2020; 32(2): 57–64. DOI: 10.1017/neu.2019.35.
19. Beauchamp TL, Childress JF. Principles of biomedical ethics, fifth ed. New York: Oxford University Press. 2001; 454 p.
20. UNESCO. Universal Declaration on Bioethics and Human Rights. Paris: UNESCO. 2005. Режим доступа: [Электронный ресурс]. URL: http://portal.unesco.org/en/ev.php-URL_ID=31058&URL_DO=DO_TOPIC&URL_SECTION=201.html (дата обращения 10.03.2024).
21. Rinck PA. Magnetic Resonance in Medicine. A Critical Introduction. The Basic Textbook of the European Magnetic Resonance Forum. 2023. Режим доступа: [Электронный ресурс]. URL: https://www.trtf.eu/pubs/Textbook_AdvancedContrast.pdf (дата обращения 10.03.2024).
22. Karmarkar UR and Yoon C. Consumer neuroscience: advances in understanding consumer psychology. Current Opinion in Psychology. 2016; 10: 160–165. DOI: 10.1016/j.copsyc.2016.01.010.
23. Spear LP. Adolescent neurodevelopment. Journal of adolescent health. 2013; 52(2): 7–13.
24. UN. Declaration on the commemoration of the seventy-fifth anniversary of the United Nations, United Nations General Assembly. A/RES/75/1. 2020. Режим доступа: [Электронный ресурс]. URL: https://unacov.uk/un75-declaration/ (дата обращения 10.03.2024).
25. UN. Our Common Agenda, report of the Secretary-General. 2021. Режим доступа: [Электронный ресурс]. URL: https://web.archive.org/web/20230216065407/; https://www.un.org/en/content/common-agenda-report/ (дата обращения 10.03.2024).
26. UNESCO. University of Milan-Bicocca (Italy) and State University of New York — Downstate Health Sciences University. The risks and challenges of neurotechnologies for human rights. 2023. Режим доступа: [Электронный ресурс]. URL: https://unesdoc.unesco.org/ark:/48223/pf0000384185.page=%5B8%5D (дата обращения 10.03.2024).
27. Zúñiga-Fajuri A, Miranda LV, Miralles DZ, Venegas, RS. Neurorights in Chile: Between neuroscience and legal science. Developments in Neuroethics and Bioethics. 2021; 4: 165–179.
28. Government of France. Charter for the Responsible Development of Neurotechnologies. Ministry of Higher Education and Research. 2022. Режим доступа: [Электронный ресурс]. URL: https://www.enseignementsup-recherche.gouv.fr/fr/charte-de-eveloppement-responsable-des-neurotechnologies-87964 (дата обращения 10.03.2024).
29. Government of Spain. Charter of Digital Rights.pdf. 2021. Режим доступа: [Электронный ресурс]. URL: https://portal.mineco.gob.es/RecursosArticulo/mineco/ministerio/participacion_publica/audiencia/ficheros/Charter%20of%20Digital%20Rights.pdf (дата обращения 10.03.2024).
30. UK's Information Commissioner's Office ICO tech futures: neurotechnology: Regulatory issues. ICO. 2023. Режим доступа: [Электронный ресурс]. URL: https://ico.org.uk/about-the-ico/research-and-reports/ico-tech-futures-neurotechnology/regulatory-issues/ (дата обращения 10.03.2024).

ETHICAL AND LEGAL ASPECTS OF ADMINISTRATION OF ANTIBACTERIAL RESERVE PREPARATIONS

Yarovoy SK ✉

Research Institution of Urology and Interventional Radiology named after Lopatkin NA, Moscow, Russia

The article explains what an antibacterial reserve preparation means. It has been shown that the drug belonging to the group is determined by its pharmacological properties only such as a clinically significant (sufficient for empirical application) activity in relation to Pseudomonas aeruginosa or nosocomial (methicillin-resistant) strains of Staphylococcus aureus. It allows to differentiate between two categories of reserve antibiotics, which exert an anti-Gram-negative and anti-Gram-positive activity. There is an exhaustive list of preparations included into each group and available in the Russian market. Meanwhile, no drugs that correspond to inclusion requirements for both groups are available. Possible conflicts that occur during clinical application of antibacterial reserve drugs are comprehensively analyzed. It is based on divergence of interests of a patient and the patient's representatives, treating physician, management of the clinic, hospital epidemiologists and manufacturers of reserve generics. Economic and general biological (selection of drug-resistant strains in extensively wide application) arguments commonly contradict the legal (compliance with clinical recommendations), moral and ethical (independence of aid quality from the patient's prognosis) standards. The Legislator's position in relation to the issue has been reviewed. Imperfect regularity framework and insufficient legal safety of a doctor make it possible to resolve conflicts through concessions and agreements including reserve antibiotics prescribed as per conditionally social indications.

Keywords: antimicrobial therapy, reserve antibiotics, selection of polyresistant strains

✉ **Correspondence should be addressed:** Sergey K. Yarovoy
3rd Parkovaya Str., 51/4, Moscow, 105425, Russia; yarovoy.sk@yandex.ru

Received: 19.02.2024 **Accepted:** 29.02.2024 **Published online:** 16.03.2024

DOI: 10.24075/medet.2024.003

ЭТИЧЕСКИЕ И ЮРИДИЧЕСКИЕ АСПЕКТЫ НАЗНАЧЕНИЯ АНТИБАКТЕРИАЛЬНЫХ ПРЕПАРАТОВ РЕЗЕРВА

С. К. Яровой ✉

НИИ урологии и интервенционной радиологии им. Н. А. Лопаткина, г. Москва, Россия

В статье разъяснено понятие антибактериального препарата резерва. Показано, что принадлежность лекарственного средства к этой группе определяется исключительно его фармакологическими свойствами — клинически значимой (достаточной для эмпирического применения) активностью в отношении *Pseudomonas aeruginosa* или нозокомиальных (метициллинрезистентных) штаммов *Staphylococcus aureus*. Это позволяет выделить две категории резервных антибиотиков — соответственно «антиграмотрицательные» и «антиграмположительные». Приведен исчерпывающий перечень препаратов, входящих в каждую из групп и представленных на отечественном рынке. При этом лекарственные средства, отвечающие требованиям включения одновременно в обе группы, отсутствуют. Всесторонне проанализированы возможные конфликтные ситуации, возникающие при клиническом применении антибактериальных препаратов резерва. В их основе лежит расхождение интересов пациента и его представителей, лечащего врача, администрации клиники, больничного эпидемиолога и производителей дженериков препаратов резерва. Экономические и общебиологические (селекция лекарственноустойчивых штаммов при чрезмерно широком применении) аргументы нередко входят в противоречия с аспектами юридическими (следование клиническим рекомендациям) и нравственно-этическими (независимость качества помощи от прогноза пациента). Рассмотрена позиция Законодателя, касающаяся изучаемого вопроса. Несовершенство нормативной базы и недостаточная юридическая защищенность врача делает возможным разрешение конфликтов лишь путем уступок и договоренностей, в том числе и за счет назначения резервных антибиотиков по условно «социальным» показаниям.

Ключевые слова: противомикробная терапия, антибиотики резерва, селекция полирезистентных штаммов

✉ **Для корреспонденции:** Сергей Константинович Яровой
ул. Парковая 3-я, д. 51, стр. 4, Москва, 105425, Россия; yarovoy.sk@yandex.ru

Статья поступила: 19.02.2024 **Статья принята к печати:** 29.02.2024 **Опубликована онлайн:** 16.03.2024

DOI: 10.24075/medet.2024.003

THE NOTION OF A RESERVE ANTIBIOTIC

In real clinical practice, the term 'reserve antibiotics' is occasionally defined in a broad and obscure way. Novel, highly effective and, thus, cheap antibacterial agents are considered as reserve ones by the hospital management. To restrict their widely application. Reserve drugs commonly include costly medicinal products.

However, logical inconsistencies appear immediately. If the medicinal product belongs to the group of reserves due to its cost, it is not clear which threshold limit, when exceeded, turns the basic drug into the reserve one. Nobody has ever named and will hardly name any specific numbers. It is because the modern pharmaceutical market offers numerous antimicrobial generics, including very cheap ones. It can occur that medicinal agents with the same active substance produced by various manufacturers who offered different prices for the product can be classified both as basic and reserve preparations. It is inaccurate to believe that the antibiotics status is somehow related to the price.

From the point of view of clinical pharmacology, reserve antibiotics include the means that stay in the reserve if the pathogen is resistant to basic drugs. Thus, we can say that the drug belongs to the reserve group due to its antimicrobial activity or ability to suppress strains of pathogens with acquired resistance to drugs. Neither wide specter, nor cost of the drug can play an essential role.

A wide number of costly antibacterial agents with a wide specter of antimicrobial activity is found in the market. They are not capable to inhibit nosocomial infections. Thus, they are basic but not reserve. This is not an indicator of poor

quality but specific properties of a particular drug are inherent in the development phase. IV generation (antianaerobic) fluoroquinolones represent a classic example. Initially, their significant specter of antimicrobial activity typical of the entire pharmacological group is additionally expanded towards S. pneumonia and B. fragilis [1]. The expansion is provided at a higher cost which is quite compatible with antipseudomonal cephalosporins and cheap carbapenems. However, even novel IV generation fluoroquinolones did not become reserve ones.

Let's note the key feature of antibacterial reserve preparations.

The reserve preparation is developed to suppress microorganisms with high resistance to antimicrobial agents such as hospital or nosocomial strains. There are only two categories of reserve preparations such as anti-Gram-negative and anti-Gram-positive ones. Actual belonging of a drug to the group of reserve medicines is determined by formal features.

The agents of the anti-Gram-positive reserve should suppress methicillin(oxacilline, cefoxitin)-resistant strains of Staphylococcus (MRSA and MRSE). They include vancomycin, ceftarolin, linezolid, tigecycline, and daptomycin.

The agents of the anti-Gram-positive reserve should be active in relation to Pseudomonas aeruginosa (P. aeruginosa). These include antipseudomonal cephalosporins (ceftazidime, cefepime, cefoperazone/sulbactam, cefepime/sulbactam, ceftazidime/avibactam), antipseudomonal penicillins (piperacillin/tazobactam, ticarcillin/clavulanate), amikacin, and antipseudomonal carbapenems (meropenem, imipenem/cilastatin, doripenem).

The activity mentioned above is clinically significant and rather high to be used in the empirical mode.

The same drug can have a different status in relation to various groups of pathogens. Moreover, it seldom happens that one drug property can't be applied in clinical practice. For instance, carbapenems are not used in therapy of gram-positive infectious processes though they have a clinically significant anti-Gram-positive activity against wild strains of Staphylococcus spp. and Streptococcus spp.

CONFLICT OF INTERESTS WHILE ADMINISTERING ANTIBACTERIAL RESERVE DRUGS

From the time of occurrence and until now, antibacterial reserve drugs are the subject of endless debates and conflicts. It is natural as interests of at least five parties interact here. But total coincidence of interests is possible under no circumstances.

1. A patient who acts as a client and consumer of a medical service from the legal point of view is interested in the best effectiveness of therapy 'here, now and using any affordable means'. He is indifferent about the economic part of the issue and risk of selection of hospital strains. He does not wish to comply with profile clinical recommendations until complications or adverse effects occur. Until any risks are implemented.

It means that the patient, the patient's relatives/representatives will insist on the rapid use of reserve drugs which seem more effective to him as compared to basic ones as they are capable to suppress both wild, and hospital strains of pathogens. In contrast to basic drugs which are active against wild strains only.

The situation is aggravated by decision of the Plenum of the Supreme Court No. 1 as of 26.01.2010, where the principle of presumption of innocence for a medical organization was actually withdrawn in relation to medical matters [2]. As a result, any competent individual can write nonsense like 'the result of treatment of my elderly relative does not seem satisfactory to me because he used to be physically fit and could take care of himself, whereas now, following a stroke, he fails to understand why he should take care of himself; I believe that treatment was not provided in time and that it does not totally comply with the Clinical recommendations; and this was the reason of failure; I ask to hold XXX liable and pay me XXX RUB to compensate for moral damage'. In accordance with the acting legislation, he does not have to prove anything.

Meanwhile, nobody asked the opinion of the elderly relative who developed an acute cerebrovascular accident but was not deprived of legal capacity de ure. To initiate the check by the supervisory authority it's enough to have a detached view and a fantastic complaint.

2.Provision of a **treating physician** directly depends on satisfaction of patients. His patients. Condition of other patients and epidemiological welfare of the hospital are secondary to him. In words, it is essential. But in real life, it does not mean anything at all. A hospital doctor won't be responsible if carbapenem-resistant Klebsiella spp. are found at the hospital. An unhappy patient or relatives will write a complaint consisting of non-use or untimely (as assessed by the patient) use of any available means. Controlling companies will hardly ignore the 'insufficiently active therapy'.

Among administrators and lawyers, there is a widely spread belief that properly selected therapy should totally correspond to the current regulatory framework. The position is precarious because no regulatory framework determines therapy in the form of an order. Only regulations and limitations but not commands are provided there. This is how medical regulatory framework differs from the military regulations.

All motivating instructions related to drug-induced therapy of patients are executed as 'Recommendations', which are literally non-binding. It is obviously done so to reduce the liability of their developers. Direct compliance with profile recommendations approved by the order of the Ministry of Health of the Russian Federation or Antimicrobial Stewardship program [3] does not warrant legal safety of a treating physician for claims in case of unsuccessful treatment. Unlike military personnel, a doctor is responsible for the results of actions but not for formal adherence to the law irrespective of consequences. And if you look deeper, responsibility lies not even with administration of a drug, which constitutes a doctor's meaningful action, but with the clinical effect of the drug, which can be tried to predict but not to make! Effect of the drug is the same as effect of nature.

So, a treating physician will practice early administration of reserve antibacterial drugs using the terms 'novel', 'highly effective', etc. especially if the patient or the patient's relatives are prone to barratry.

3. An epidemiologist is interested in control over nosocomial strains of pathogens and no deaths from hospital-acquired infection. Prognosis for a certain patient or the situation surrounding the epidemiologist is definitely important but secondary.

Control over nosocomial strains de facto means that its spread is minimized. This can be achieved only with wild strains without acquired drug resistance but capable to use the living space and nutrient medium faster and more effectively. Drug-induced suppression of a certain microorganism releases the niche that will be inhabited by microorganisms which are resistant to the agent. Wild strains or strains with low resistance can survive only within the environment lacking antimicrobial agents. It means that to achieve the goals, an epidemiologist should cut the administration of all antibiotics, especially reserve drugs, which make selection of superresistant hospital strain possible.

But the only voice of an epidemiologist is nothing against that of clinicians and scandalous relatives!

4. Management of the clinic is ambivalent. On the one hand, conflicts with patients, their relatives and inspecting authorities

should be settled exclusively by diplomatic means because other options (conditionally powerful) currently remind of a suicide attack due to total disability of the entire state machine.

The definition 'we did what we could; combined therapy with the best reserve drugs was administered since the time of admission to the clinic' sounds great, it sounds fine while dealing with a low-competent partner. None of those who make arrangements is bothered by the fact that the practice makes hospital welfare doubtful.

On the other part, reserve preparations are costly. Many of them are required. Sometimes there are too many of them. In some branches of clinical medicine, for instance, pulmonary medicine, expenses on the purchase of reserve antibiotics only can exceed 80% of the total amount of drug-induced therapy financing. So, **almost any solution associated with distribution of reserve antimicrobial agents has a high economical significance**.

There are two ways how consumption of any product (or preparation) can be reduced: economy or normalized consumption. From the ethical point of view, both options are doubtful.

What do we save for? And who? 'Irrational prescription' is a common answer. The answer is neutral and, thus, has external beauty. Nevertheless, it is fatally flawed. Are employees competent enough to allow the things happen in the presence of numerous irrational prescriptions and significant economy? Can management be considered adequate if no timely interference occurred? In the presence of a few irrational prescriptions, the saved means can not even compensate for expenses on time and labor associated with searching and correction. It is not about economy. It is about imitation of economy.

In fact, we'll have to save on comorbid decompensated patients with a poor diagnosis who sometimes determine up to ¾ of total expenditure of carbapenems, antipseudomonal cephalosporins, vancomycin and linezolid at intensive care units. This totally contradicts the principles of ethics in accordance with which qualitative and adequate aid should be provided to all patients irrespective of their prognosis.

It is the same with normalized consumption. These attempts are constant and unintentional. Erratic arrival of some agents results in the following definition: 'I can provide xxx of vials with meropenem but no more, so you can distribute the available vials as you like. The preparation has already been ordered and paid for but is not available today. Nobody knows for sure whether it can be available tomorrow, the day after tomorrow or in a week. It is supplied by private companies'.

Based on the real practice, economy allows to use the critical resource in a more efficient way as compared with the consumption rate.

An epidemiologist's opinion is essential for administration as well. The idea of economy is totally supported as well. Until the first serious complaint though.

5. Pharmaceutical companies producing generics represent private companies that want profit by any legal means. The cost of an original drug used to be a very serious constraining factor. Relatively cheap generics imipenem/cilastatin, meropenem linezolide and other reserve antibitoics that can be seen in the market only increase the temptation. It is still disputable whether using cheap reserve preparations is good or bad. It seems good, and the aid becomes more affordable. However, it is bad in reality because after certain (not significant enough as carbapenem-related proper data have been obtained but are still being published) rate of administration, the reserve agent can't be classified as reserve any more, and no aid will be provided any longer. There will be what the aid can be provided with, but the aid will be simulated.

No ban, recommendation or administrative regulation can decrease the rate as effective as the cost does. Nowadays, we have come across a paradoxical situation when rarely administered due to high cost ceftazidime/avibactam (III generation inhibitory protective antipseudomonal cephalosporin which is actually an antgramnegative reserve line 1 preparation) is used to inhibit Klebsiella spp. and P. aeruginosa strains with total (!) carbapenem resistence [4,5]. It is successfully used not in casuistic cases, but with certain though small regularity (in cystic fibrosis) when combined with amikacin and sometimes as monotherapy.

The issue of antibiotics distribution is far from being settled today. The management commonly delivers it to the service of clinical pharmacology developed to deal with the issues. Unfortunately, turnover of the drugs at the medical institution can be controlled only manually under the modern conditions of imperfection of the regulatory framework.

References

1. Kinicheskaya pharmakologia. Pod redaktsiyey VG Kukesa, D. A. Sicheva M.: GEOTAR-Media. 2021; 1012 s. Russian.
2. Vrachebnie dela. Yuridicheskaya I expertnaya otcenka problem nenadlezhaschego okazania medicinskoy pomoschi. Pod redaktsiyey A. A. Mokhova. M.: Block-print; 268 s. Russian.
3. Programma SKAT (Strategia Kontrolya Antimicrobnoy Terapii) pri okazanii stacionarnoy medicinskoy pomoschi: Rossiyskiye klinicheskiye rekomendacii. Pod redaktsiyey SV Yakovleva, NI Briko, SV Sidorenko, DN Protsenko. M.: Pero. 2018; 156 s. Russian.
4. Kozlov RS, Stetsiouk OU, Andreeva IV. Ceftazidime-avibactam: new rules for the game against multidrug-resistant gram-negative bacteria. Clinical Microbiology and Antimicrobal Chemotherapy (CMAC). 2018; 20(1): 24–34 DOI: 10.36488/cmac.2018.1.24-34. Russian.
5. van Duin D, Lok JJ, Earley M, et al. Colistin versus ceftazidimeavibactam in the treatment of infections due to carbapenem-resistant Enterobacteriaceae. Clin Infect Dis. 2018; 66(2): 163–171.

Литература

1. Клиническая фармакология под ред. ак. В. Г. Кукеса, чл.-корр. Д. А. Сычева. 6-е издание, исправленное и дополненное. М.: ГЭОТАР-Медиа. 2021; 1012 с.
2. Врачебные дела. Юридическая и экспертная оценка проблем ненадлежащего оказания медицинской помощи. Монография под редакцией д.ю.н. А. А. Мохова. М.: Блок-принт; 268 с.
3. С. В. Яковлева, Н. И. Брико, С. В. Сидоренко, Д. Н. Проценко Программа СКАТ (Стратегия Контроля Антимикробной Терапии) при оказании стационарной медицинской помощи: Российские клинические рекомендации под ред. С. В. Яковлева, Н. И. Брико, С. В. Сидоренко, Д. Н. Проценко. М.: Перо. 2018; 156 с.
4. Козлов Р. С., Стецюк О. У., Андреева И. В. Цефтазидим-авибактам: новые «правила игры» против полирезистентных грамотрицательных бактерий. Клиническая микробиология и антимикробная химиотерапия. 2018; 20(1): 24–34. DOI: 10.36488/cmac.2018.1.24-34.
5. van Duin D, Lok JJ, Earley M, et al. Colistin versus ceftazidimeavibactam in the treatment of infections due to carbapenem-resistant Enterobacteriaceae. Clin Infect Dis. 2018; 66(2): 163–171.

BIOETHICAL APPROACH TO ESTIMATION OF PHARMACOEPIDEMIOLOGICAL AND PHARMACOECONOMIC ASPECTS OF PSORIASIS TREATMENT

Samarina EI, Lileeva EG ✉, Rybachkova JV

Yaroslavl State Medical University, Yaroslavl, Russia

Bioethical approach to determine the feasibility of using medicines involves systemic analysis of pharmacoepidemiological and pharmacoeconomic aspects of treatment, especially while treating the most common and chronic diseases. Psoriasis is the most common disease of the skin and subcutaneous tissue, accounting for 15% of cases. The rate of psoriatic complications constitutes 6–42%. Skin lesions, psoriatic arthritis, cardiovascular diseases, metabolic syndrome, inflammatory intestinal diseases, mental disorders and malignant lesions produce a great effect on health, duration and quality of life, and result in early loss of labor capacity and disability of patients. So, it is important to study effectiveness and safety of systemic medicines in patients with severe and moderate-to-severe disease and perform subsequent analysis of possible use and comparison of the effectiveness of various combinations. Most affordable but ineffective medicines commonly cause real growth of further expenses on treatment, and postpone administration of more effective, though much more expensive medicines. Economic aspects of rational use of healthcare resources are becoming increasingly important whereas pharmacoeconomic values are crucial while selecting a treatment strategy.

Keywords: psoriasis, pharmacoeconomics, genetically engineered biological drugs, NNT (number needed to treat), CpR (cost per responder), methotrexate

Author contribution: the authors reviewed literature data regarding the study of pharmacoepidemiological and pharmacoeconomic aspects of psoriasis treatment. The authors have made equal contributions into writing the article.

✉ **Correspondence should be addressed:** Elena G. Lileeva
Revolutsionnaya Str., bld. 5, Yaroslavl, 150000, Russia; elileeva2006@yandex.ru

Received: 24.01.2024 **Accepted:** 20.02.2024 **Published online:** 11.03.2024

DOI: 10.24075/medet.2024.001

ФАРМАКОЭПИДЕМИОЛОГИЧЕСКИЕ И ФАРМАКОЭКОНОМИЧЕСКИЕ АСПЕКТЫ ЛЕЧЕНИЯ ПСОРИАЗА

Е. И. Самарина, Е. Г. Лилеева ✉, Ю. В. Рыбачкова

Ярославский государственный медицинский университет, Ярославль, Россия

Среди болезней кожи и подкожной клетчатки псориаз является самым распространенным заболеванием, на долю которого приходится 15%. Частота псориатических осложнений при псориазе составляет 6% — 42%. Поражения кожи, псориатический артрит, сердечно-сосудистые заболевания, метаболический синдром, воспалительные заболевания кишечника, психические расстройства и злокачественные новообразования оказывают большое влияние на состояние здоровья, продолжительность и качество жизни, приводят к преждевременной потере трудоспособности и инвалидизации больных. Поэтому огромное значение приобретают клинико-экономические аспекты лечения бляшечного псориаза и его сопутствующих проявлений, а именно оценка расходов пациентов и их ближайших родственников, инвалидизация пациентов и затраты на амбулаторное и стационарное лечение.

Ключевые слова: псориаз, фармакоэкономика, генно-инженерные биологические препараты, NNT (number needed to treat), CpR (cost per responder), метотрексат

Вклад авторов: авторами проведен обзор литературных данных по тематике исследования в области фармакоэпидемиологических и фармакоэкономических аспектов лечения псориаза. Авторы внесли равный вклад в написание статьи.

✉ **Для корреспонденции:** Елена Георгиевна Лилеева
ул. Революционная, д. 5, г. Ярославль, 150000, Россия; elileeva2006@yandex.ru

Статья поступила: 24.01.2024 **Статья принята к печати:** 20.02.2024 **Опубликована онлайн:** 11.03.2024

DOI: 10.24075/medet.2024.001

Psoriasis is a systemic immune-mediated multifactorial disease, which occupies an important position in the structure of skin diseases and is associated with a dominant value in the development of genetic factors characterized by an accelerated proliferation of keratinocytes and their disturbed differentiation, and imbalance between pro- and anti-inflammatory cytokines with frequent abnormal changes of the locomotor apparatus [1, 2].

Psoriasis is a common skin and subcutaneous disease. The proportion of patients with psoriasis reaches 15% [3]. According to the WHO, 125 million people around the globe suffer from the disease [4]. In 2018, prevalence of psoriasis in Russia was 0.24% (356,030 people) [1]. In 2018, diseases of skin and subcutaneous tissue rank 4th in the structure of morbidity in the Russian Federation [3].

The rate of psoriatic complications constitutes 6–42% [5]. Severe and moderate-to-severe diseases are found in 20% and 30% of cases, respectively [6]. Skin lesions, psoriatic arthritis, cardiovascular diseases, metabolic syndrome, inflammatory intestinal diseases, mental disorders and malignant lesions produce a great effect on health, duration and quality of life, and result in early loss of labor capacity and disability of patients. Thus, clinical and economic aspects of treatment of plaque psoriasis and its respective complications, namely, assessment of expenses borne by patients and closest relatives, disability of patients and expenses on outpatient and inpatient treatment are of significant importance.

The problems of plaque psoriasis therapy are associated with a delayed complex approach of prescribing drugs,

correction of many concomitant diseases and low adherence to treatment. Quality of life and neurological anxiety-depressive disorders are crucial while assessing health, effectiveness and safety of drug-induced therapy in long-term treatment of chronic diseases, particularly, plaque psoriasis combined with psoriatic arthritis. The last ones are taken as factors that do not only accompany the somatic well-being but also worsen the course of diseases and quality of life [7]. Thus, a complex analysis of drug-induced therapy obtained by patients with plaque psoriasis and concomitant psoriatic arthritis seems to be a pressing issue, solution of which promotes a favorable course of the disease taking into account the clinical and economic constituent.

Control over the process of rendering medical services does not guarantee success. Clinical research only without generalization of results fail to effectively contribute to the use of healthcare resources due to a physical impossibility to comprehend enormous amounts of information. As no work associated with clinical and economic studies is coordinated and carefully targeted, they are all separated now and devoted to various narrow topics such as the use of a certain drug in a certain dosage within a certain group of patients with various confounding factors.

Moreover, significantly different methods described in various works hamper result generalization as the medicines are used in a variety of dosages and duration of observation of patients varies as well. To sum up, the results of different works are incomparable and the volume of information is significantly increased. Thus, neither attending physician nor administrator has enough time to trace and estimate the available level of evidence regarding treatment methods even if it was filtered out using meta-analyses as the data of direct comparative studies are limited. Special mechanisms that would allow to supply doctors with reliable information about the methods with proven effectiveness and safety are required [8].

Clinical recommendations, which were last revised in 2023, were considered as a required tool of managing patients with plaque psoriasis. They were a means that support taking clinical solutions or mechanism of regulation of expenses as they described therapy priority and linearity.

Almost 70–80% of patients have mild psoriasis, which can be treated with local therapy [7]. Mild psoriasis is determined taking into account 10% of the affected body surface area (BSA), Psoriasis Area and Severity Index (PASI) (10 scores), and Dermatological Quality of Life Index (DQLI). Psoriasis is classified as moderate and severe if BSA >10% or PASI >10 and DLQI >10 scores and if it corresponds to one or several increasing criteria such as distinct affection of visible areas, scalp, genitals, palms and soles, psoriasis of nails, itching and stable plaques.

According to advanced guidelines that have been revised during the last ten years, therapy goals included skin cleansing by 90–100% as compared with the initial value (PASI 90, PASI 100) (National Psoriasis Foundation) [9] and global estimation by an investigator at the level of 0–1 scores (PGA 0–1) (Societe Francaise de Dermatologie) [10].

The latest recommendations of the Japanese Association of Dermatologists of 2020 include the DLQI (0/1 scores) [10].

The latest clinical recommendations on psoriasis as of 2023 contain a clear algorithm of selecting a therapeutic direction (fig.). In case of limited eruptions, external therapy is applied, whereas systemic therapy is used in extensive eruptions.

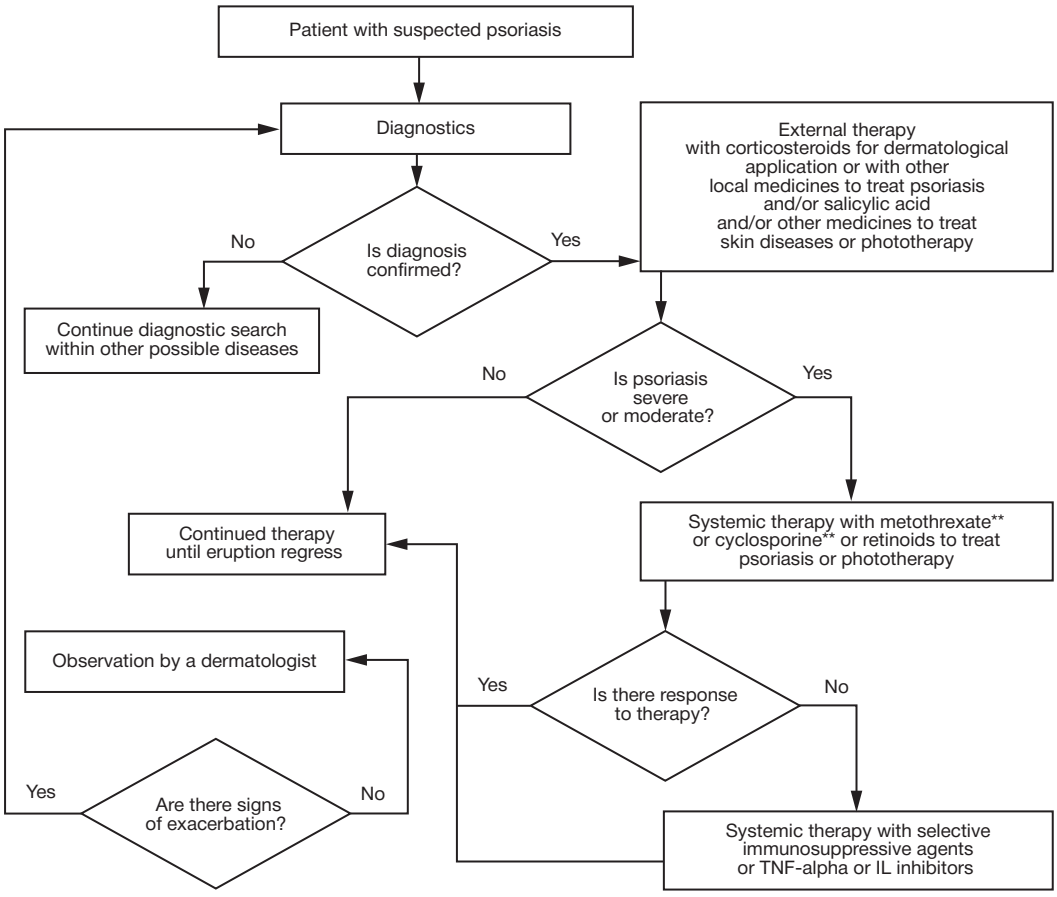

Fig. Algorithm of managing patients with psoriasis as per the latest clinical recommendations (2023).

Systemic therapy includes systemic immunosuppressive agents (including systemic photochemotherapy), Janus kinase inhibitors and genetically engineered biological agents. Systemic glucocorticoids are used in some conditions (generalized pustular psoriasis, psoriatic erythroderma).

In accordance with clinical recommendations, moderate-to-severe and severe psoriasis is treated with the following agents [1, 11]:

- systemic immunosuppressive agents (cyclosporine, methotrexate, acitretin, apremilast, systemic photochemotherapy);
- Janus kinase inhibitors (Tofacitinibum);
- genetically engineered biological agents such as TNF inhibitors (Infliximab, adalimumab, etanercept, certolizumab pegol), IL-12/23 ustekinumab, IL-17 (secukinumab, ixekizumab, netakimab), IL-23 (guselkumab, risankizumab).

Burden of comorbidities is growing during the life of a patient with psoriasis. The issue of accumulated influence of a disease on a patient's life and health is being actively discussed. The volume of accumulated burden results in stable psychosocial and personal disturbances. It makes human health irreversibly altered. An earlier diagnostics of psoriasis subtype and timely beginning of pharmacotherapy with properly selected medicines can slow disease progression and prevent social isolation of patients. It should be noted that modern genetically engineered drugs have an ethical advantage as patients can get acquainted with open-source data beforehand and expect clinical effectiveness to be obtained in quite a short time as compared with standard therapy, for instance, with methotrexate, ciclosporin and retinoids. On the other hand, it does not mean that a patient with burdened disease progression independently solves complex clinical and ethical issues and estimates benefit, harm, and safety of therapy suggested by a doctor. All clinicians are advised to act in accordance with clinical recommendations without skipping the graduation and priority of therapy. Progress in the development and registration of novel short-acting drugs raises numerous ethical issues. The issues are about how to balance and protect this group of patients from possible risks associated with increased emotional dissatisfaction with consistent therapy when genetically engineered drugs represent the last hope. Anonymity and confidentiality belong to other ethical issues of treating patients with psoriasis. Many employed patients prefer not to inform the employer of their disease. This makes them search for the most effective methods of treatment independently and discuss such an administration with the treating physician ignoring the legally adopted step therapy.

SYSTEMIC IMMUNOSUPPRESSIVE AGENTS

Methotrexate is considered as a highly effective agent to treat common psoriasis, psoriatic erythroderma, pustulous and arthropathic psoriasis.

Zilberberg NV and Kokhan MM analyzed their experience of treating psoriasis with methotrexate, a golden standard of systemic therapy, administered by intramuscular and subcutaneous injections [12]. The submitted results of using methotrexate in therapy of patients with moderate-to-severe and severe psoriasis administered by subcutaneous injections as compared with intramuscular injections demonstrated a highly effective course of treating psoriasis and psoriatic arthritis with methotrexate. The data regarding a higher safety, a more significant positive influence on life quality, better tolerance and a longer remission were achieved within a group of patients administered subcutaneous injections of methotrexate.

Methotrexate (4-amino-10-methyl-folic acid) belongs to a group of cytostatic agents and is an antagonist of folic acid. In the clinical setting, the preparations are combined. Methotrexate competitively inhibits dihydrofolate reductase and some pholate dependent enzymes resulting in suppressed synthesis of nucleic acids and, ultimately, DNA and RNA synthesis suppression. Meanwhile, nucleic acid synthesis is suppressed in every dividing cell of gastrointestinal tract, liver, immune system and skin [13]. Methotrexate inhibits production of inflammation mediators such as leukotrienes, TNF-α, IL-1β and adhesion molecules (E-selectine and VCAM-1) and prevents adhesion of white cells to the vascular endothelium.

According to literature, methotrexate therapy decreased the percentage of TNF-positive CD4+ T cells in the peripheral blood of patients with rheumatic disease but increased the number of IL-10-positive T-cells [12, 13].

According to the latest clinical recommendations, patients with plaque psoriasis are administered methotrexate if systemic therapy is indicated (in case of resistance to the conducted external therapy and in common moderate or severe rashes) [14].

At the same time, according to Gallyamov YuA and Asokov AV, long-term therapy with methotrexate allows to claim its effectiveness in patients with psoriasis and psoriatic arthritis. However, the possibility of adverse events including hepatoxicity, anemia and neutropenia, gastrointestinal events (nausea, vomiting, stomatitis, loss of appetites) is not excluded. This decreases therapy compliance and limits its use [15].

Cyclosporine is one of the best-known drugs to treat psoriasis, which produces not only an anti-inflammatory but also a cytostatic effect. The drug has a narrow therapeutic window. Regular control of plasma creatinine is required as a nephrotoxic effect, blood pressure rise, changes in the level of potassium, uric acid, bilirubin, transaminase, and lipid profile are possible. The drug should be withdrawn on a constant basis. Due to cytostatic and immunosuppressive effects, treatment with cyclosporine increases the risk of lymphoproliferative diseases and other malignant lesions, especially those of the skin [15].

JANUS KINASE INHIBITORS

Tofacitinibum was the first Janus kinase inhibitor registered for treatment of plaque psoriasis ad psoriatic arthritis (PsA). Effectiveness and safety of tofacitinibum at doses of 5 and 10 mg BID for PsA treatment was studied in two placebo-controlled studies in 710 patients with no response to standard DMARDs (ORAL Broaden) and combination therapy with DMARDs and TNF-α inhibitors (ORAL Beyond) [16]. In the both studies, Janus kinase inhibitors were combined with DMARDs and methotrexate, in particular. During the ORAL Broaden study, a group of patients obtained adalimumab. In 3 months, the rate of response by AKP20 criteria was significantly higher in the tofacitinibum group (50.0–53.0%) as compared to placebo (28.0%). Similar results were obtained when the response was analyzed by AKP50 and AKP70 criteria. Moreover, treatment with tofacitinibum resulted in a more significant improvement of the functional activity of patients assessed based on HAQ-DI and a decreased number of tender and swollen joints. Advantage of tofacitinibum over placebo was recorded when effectiveness of psoriasis, enthesitis, dactylitis and spondylitis (BASDAI) treatment was assessed. In the ORAL Broaden study, no significant difference was found for tofacitinibum as compared with adalimumab.

GENETICALLY ENGINEERED BIOLOGICAL AGENTS (GEBAS)

GEBAs are third-line agents for patients with psoriasis. Genetically engineered biological therapy is indicated to patients with psoriasis and psoriatic arthritis in the following cases:

1) in the presence of comorbid and concomitant diseases that make it impossible to use a standard systemic immunosuppressive therapy;
2) in the presence of active progressive psoriatic arthritis with factors of unfavorable prognosis, high activity spondylitis combined with functional disturbances and ineffective standard therapy of NSAIDs at therapeutic doses; polyarthritis with joint erosion, functional disturbances if standard therapy is not effective; multiple enthesitis and dactylitis with functional disturbances refractory to standard therapy;
3) in certain (problematic) location of psoriatic elements (exposed skin, genitals, palms and soles; pronounced psoriatic onychodystrophy) and a significant decrease of life quality (DLQI > 15) [12].

Nowadays, TNF-α inhibitors, interleukin 17 inhibitors, interleukin 12/23 inhibitors, and interleukin 23 inhibitors are approved to treat moderate to severe psoriasis. Low-molecular inhibitors such as apremilast and deucravacitinib are also approved to treat psoriasis [1]. Nevertheless, it is not clear yet how systemic agents to treat psoriasis influence concomitant diseases by changing the systemic inflammation.

Data of clinical trials of safety and effectiveness of biological preparations and low-molecular inhibitors are important for a personalized approach to treatment of patients with psoriasis. Notably, treatment with IL-17 inhibitors is associated with new onset or exacerbation of an inflammatory bowel disease.

Nevertheless, more caution should be taken while using TNF-α inhibitors in patients with psoriasis and concomitant congestive cardiac failure, disseminated sclerosis and malignant lesions. Apremilast can result in the loss of weight as an adverse effect and also produce some positive metabolic effect [4].

It is necessary to consult a TB specialist prior to administration of GEBAs and during therapy with GEBAs. Reactivation of mycobacterial infection with TB of lungs and other organs is possible against the background of therapy with TNF-α or IL inhibitors as immunosuppressive action of drugs and activation of mycobacterial infection with a higher risk as compared with TNF-α inhibitors can be recorded [17–22].

The most commonly administered drugs include the ones inhibiting effectory interleukins 17 such as Netakimab, Secukinumab, Ixekizumab with a similar mechanism of action and drugs inhibiting regulatory IL-23, in particular, Guselkumab and Risankizumab.

Secukinumab is a human monoclonal IgG1k antibody that has been developed to target and block the actions of IL-17A. This is how its binding with receptors and stimulated expression of pro-inflammatory genes are prevented [19].

The most common adverse events while taking secukinumab included infections of the upper respiratory tracts, oral herpes, ringworm of foot, rhinitis, and diarrhea [23].

Guselkumab is intended to treat moderate-to-severe and severe plaque psoriasis in adults who are receiving systemic therapy. Guselkumab as monotherapy and combined with methotrexate is indicated to treat active psoriatic arthritis in adults with insufficient response or intolerance of previous therapy with basic anti-inflammatory agents. In psoriasis, guselkumab is generally administered as 100 mg subcutaneous injections at Week 0, Week 4, then every 8 weeks.

Risankizumab is a fully human IgG monoclonal antibody that binds with high affinity to the p19 sub-unit of IL-23. In phase 3 clinical psoriasis trials, neither of 72 participants with latent TB who were administered Risankizumab and obtained proper preventive TB therapy developed an active form of TB within 61 weeks of follow-up against therapy with risankizumab [24]. None of 31 patients with latent TB involved in the IMMHANCE study who failed to obtain preventive TB treatment developed active TB within 55 weeks of therapy with Risankizumab [24]. Up to 16 weeks safety of risankizumab was analyzed in the integrated data from the placebo- or active-comparator studies. Serious adverse events occurred in 2.4% of patients with Risankizumab as compared with 4.0% in placebo group and 5.0% in the group of ustekinumab.

Anti-TB therapy should be considered prior to initiating guselkumab in patients with a past history of latent or active TB in whom an adequate course of treatment is not confirmed [25]. No active form of TB developed within a 43-week observational period of clinical studies involving 105 subjects with latent TB who were administered guselkumab and concomitant preventive therapy.

PHARMACOECONOMIC ANALYSIS OF PSORIASIS THERAPY

Active development of biotechnologies provided a rather wide access to biological agents for psoriasis treatment. Thus, an optimal choice of therapy acquires a great importance.

In the works of Bakuleva AL and Mladova VV, effectiveness and safety of biological and synthetic medicinal agents were accessed based on NMA (network-meta-analysis) methodology [26]. The goal of this study was to determine the value of NNT (number needed to treat) and respective CpR (cost per responder) value based on PASI 75/90 criteria following 12 weeks and one year of therapy for every targeted drug such as adalimumab, apremilast, ixekizumab, guselkumab, infliximab, netakimab, secukinumab, tofacitinib, ustekinumab, certolizumab pegol, tofacitinib and etanercept.

It should be noted that NNT index has been proposed as an effect indicating a number of patients who should be treated to achieve an additional expected outcome, whether a positive or a negative, as compared with another drug within the reviewed interval of time. CpR characterizes expenses on the same response to therapy within the reviewed interval and represents the result of effect multiplied by the cost of therapy with any medicinal agent in one patient.

The analysis of NNT and CpR indexes has shown that netakimab is the most economically effective therapy option in moderate-to-severe and severe plaque psoriasis as assessed by PASI 75/90 both in the short-term 12-week, and long-term 52-week periods [26].

In the scientific work by Rudakova AV and Tolkachyova DG, netakimab has shown a higher clinical and economic effectiveness as compared with other GEBAs. According to analytics, the use of netakimab in the therapeutic practice of psoriatic arthritis will decrease the load onto the healthcare budget by 21.1% during 3 years. And even if the healthcare system budget is preserved, a number of patients who can be cured during 3 years will be increased by 26.7% [27].

According to research data of Nasonov VA Research Institute of Rheumatology, economic advantages of secukinumab are presented as compared with TNF inhibitors and ustekinumab [28].

The goal of another research paper was to study possible localization of manufacture of drugs based on monoclonal antibodies in the lyophilized form. The market of medicines based on monoclonal antibodies in the lyophilic form manufactured in the Russian Federation demonstrated a significant growth from 2016 to 2020. In money term, the production increased from 1,997 to 7,589 bln RUB accounting for 20% and 45% respectively. It was established during the analysis that the period of patent protection of such international nonproprietary names as basiliximab, infliximab, omalizumab, and trastuzumab has expired. Researchers also analyzed the market structure of drugs based on monoclonal antibodies. It was found out that all medicines based on monoclonal antibodies are included into the list of vital and essential drugs the price formation of which is regulated by the country. The absolute volume of state financing of medicines based on monoclonal antibodies increased from 9,928 to 16,801 bln RUB from 2016 to 2020 [29]. One of ultimate observations of researchers from Saint-Petersburg Chemical and Pharmaceutical University of the Ministry of Health of Russia was to increase sales of localized drugs based on monoclonal antibodies in the lyophilic form in natural and money terms in a significant remaining localization potential [29].

In accordance with the results of a systematic review of effectiveness of targeted agents in the therapy of adults with severe-to-moderate and severe vulgar psoriasis in Russia by PASI 75, i.e. skin cleansing by 75% as compared with the initial result, risankizumab and ixekizumab were significantly more superior to all TNF-α inhibitors (infliximab, adalimumab and etanercept), small molecules (tofacitinib, apremilast) and IL-12/23 inhibitor ustekinumab, whereas netakimab and guselkumab had a comparable effectiveness with infliximab and were superior to the remaining drugs [30]. All TNF-α inhibitors had comparable effectiveness.

While using guselkumab, ixekizumab, infliximab, netakimab, risankizumab and secukinumab, at least two or no more than three patients by PASI 90 should be treated to achieve the same response with PASI 75 (along the upper border of 95% credible interval). Just like in the majority of previously published studies, the use of netakimab allowed for less expenses on achievement of the same response both during 12 weeks, and during one year of therapy.

Based on the results of updated network meta-analysis, IL-17 netakimab, ixekizumab, IL-23 guselkumab and risankizumab demonstrated high effectiveness as compared to other target drugs to treat vulgar psoriasis both by the percentage of patients who achieved PASI 75 and by other outcomes (PASI 90/100, PGA/IGA 0/1, DLQI) following 12 weeks of therapy [30]. Meanwhile, netakimab demonstrated a smaller CpR index by PASI 75/90 following 12 and 52 weeks of therapy [30].

CONCLUSION

The urgency of pharmacotherapy of plaque psoriasis is due to a necessary constantly improved approaches to the rational use of medicines in accordance with clinical recommendations and WHO recommendations as a main component of the national drug-induced policy. Rational pharmacotherapy produces a significant effect not only on a patient's life quality, but also on treatment cost including therapy-related expenses borne by a patient, and the state. As far as novel genetically engineered medicines acting on different targets of psoriasis go, there are no convincing data that confirm effectiveness of using various classes of systemic agents in patients with plaque psoriasis. Economic aspects of rational use of healthcare resources are becoming increasingly important whereas pharmacoeconomic values are crucial while selecting a treatment strategy. Use of most affordable but ineffective medicines commonly causes real growth of further expenses on treatment, and postpones administration of more effective though much more expensive medicines.

Thus, examination of clinical and economic aspects of psoriasis therapy is the most important constituent while providing qualitative medical aid to patients with such a disease. It is of a greater interest in the modern medical society.

References

1. Klinicheskiye rekomendatsii «Psoriaz». Available from URL: http://cr.rosminzdrav.ru/#!/recomend/866 (accessed 15.12.2023). Russian.
2. Fedotova VP, Dyudyuna AD, Stepanenko VI. Dermatovenerologiya. Uchebnoye posobiye dlya vrachey i vrachey-internov. Izd. 2-ye. rus. Dnepropetrovsk — Kiyev. Izd-vo «Svidler AL». 2011; 652 s. Russian.
3. Vsemirnyy doklad o probleme psoriaza. Available from URL: https://apps.who.int/iris/handle/10665/204417 (accessed 15.12.2023). Russian.
4. Kubanov AA, Bogdanova Ye V. «Epidemiologiya psoriaza sredi naseleniya starshe trudosposobnogo vozrasta i ob"yemy okazyvayemoy spetsializirovannoy meditsinskoy pomoshchi bol'nym psoriazom v Rossiyskoy Federatsii v 2010–2019 g.». Vestnik dermatologii i venerologii. 2020; 96(5): 07–18. DOI: 10.25208/vdv1171-2020-96-5-07-18
5. Mease PJ, Gladman DD, Papp KA, et al. Prevalence of rheumatologist-diagnosed psoriatic arthritis in patients with psoriasis in European/North American dermatology clinics. Journal of the American Academy of Dermatology. 2013; 69(5): 729–735.
6. Armstrong AV, Rid S. Patofiziologiya, klinicheskaya kartina i lecheniye psoriaza: obzor. Dzhey Am Med Assots. 2020; 323(19): 1945–1960. Russian.
7. Ramik L, Sator P. Mestnoye lecheniye vul'garnogo psoriaza. JDDG: Zhurnal Deutschen Dermatologischen Gesellschaft. 2023; 21: 631–642. DOI: 10.1111/ddg.15042
8. Gerasimov VB, Khokhlov AL, Karpov OI. Farmakoekonomika i farmakoepidemiologiya — praktika priyemlemykh resheniy. 2005; 1: 14–15. Russian.
9. Ohata C, Ohyama B, Katayama E, et al. Real-world efficacy and safety of interleukin-17 inhibitors for psoriasis: a single-center experience. J Dermatol. 2020; 47(4):405–408. DOI: 10.1111/1346-8138.15247.
10. Hayashida K, Murakami G, Matsuda S, et al. History and profile of diagnosis procedure combination (DPC): development of a real data collection system for acute inpatient care in Japan. J Epidemiol. 2021;31(1):1–11. DOI: 10.2188/jea. JE20200288.
11. Dovzhanskiy SI, Utts SR. Psoriaz ili psoriaticheskaya bolezn' v 2-kh ch. Saratov. Izd-vo Saratovsk. un-ta. 1992;(1): 176 s.; 1992;(1): 96. Russian.
12. Zil'berberg NV, Kashcheyeva YaV, Kiseleva NV, Kokhan MM. Opyt terapii bol'nykh psoriazom preparatom metotreksat v forme podkozhnykh i vnutrimyshechnykh in"yektsiy. Available from URL: https://www.lvrach.ru/2021/11/15438141(accessed 15.12.2023). Russian.
13. Nast A, Al'tenburg A, Ogyusten M, et al. Nemetskoye rukovodstvo S3 po lecheniyu obyknovennogo psoriaza, adaptirovannoye iz EuroGuiDerm. Tseli lecheniya i rekomendatsii po lecheniyu. J Dtsch Dermatol Ges. 2021;19(6):934–1150. Russian.
14. Langenbrukh A, Radtke MA, Yakobi A, et al. Kachestvo lecheniya psoriaza v Germanii: rezul'taty natsional'nogo issledovaniya zdravookhraneniya «PsoHealth3». Arka Dermatol Res. 2016;308(6):401–408. Russian.

15. Gallyamova YuA, Asoskova AV. Metotreksat v dermatologii: ot teorii k praktike. Lechashchiy Vrach. 2021; 5 (24): 46–51. Russian.
16. Nash P, Coates LC, Fleischmann R, et al. Efficacy of tofacitinib for the treatmentof psoriatic arthritis: Pooled analysis of two phase 3 studies. Rheumatol Ther. 2018;5(2):567–82.
17. Instruktsiya po meditsinskomu primeneniyu preparata Skayrizi. Available from URL: http://grls.rosminzdrav.ru/Default dostup 01.07.2023. (accessed 15.12.2023). Russian.
18. Instruktsiya po meditsinskomu primeneniyu preparata Gusel'kumab. Available from URL: http://grls.rosminzdrav.ru/Default dostup 01.07.2023 (accessed 15.12.2023). Russian.
19. Instruktsiya po meditsinskomu primeneniyu preparata Sekukinumab. Available from URL: http://grls.rosminzdrav.ru/Default dostup 01.07.2023. (accessed 15.12.2023). Russian.
20. Instruktsiya po meditsinskomu primeneniyu preparata Netakimab. Available from URL: http://grls.rosminzdrav.ru/Default dostup 01.07.2023. (accessed 15.12.2023). Russian.
21. Instruktsiya po meditsinskomu primeneniyu preparata Iksekizumab. Available from URL: http://grls.rosminzdrav.ru/Default dostup 01.07.2023. (accessed 15.12.2023). Russian.
22. Instruktsiya po meditsinskomu primeneniyu preparata Adalimumab. Available from URL: http://grls.rosminzdrav.ru/Default dostup 01.07.2023. (accessed 15.12.2023). Russian.
23. Perrone V, Losi S, Filippi E, et al. Analysis of the pharmacoutilization of biological drugs in psoriatic arthritis patients: a real-world retrospective study among an Italian population. Rheumatol Ther. 2022;9(3):875–890. DOI: 10.1007/s40744-022-00440-1.
24. Colombo D, Bianchi L, Fabbrocini G, et al. Real-world evidence of biologic treatments in moderate-severe psoriasis in Italy: results of the CANOVA study. Dermatol Ther. 2022;35(1):15166.
25. Xu C, Teeple A, Wu B, et al. Treatment adherence and persistence of seven commonly prescribed biologics for moderate to severe psoriasis and psoriatic arthritis in a U.S. commercially insured population. J Dermatolog Treat. 2022; 33(4): 2270–2277. DOI: 10.1080/09546634.2021.1950600
26. Tolkacheva DG, Sokolova VD, Mladov VV. Effektivnost' i bezopasnost' targetnykh lekarstvennykh preparatov v terapii vzroslykh patsiyentov so srednetyazhelym i tyazhelym vul'garnym psoriazom v RF. Meditsinskiye tekhnologii. Otsenka i vybor. 2019; 4:76–86. Russian.
27. Rudakova AV, Tolkacheva DG, Sokolova VD. Farmakoekonomicheskiye aspekty terapii psoriaticheskogo artrita srednetyazheloy i tyazheloy stepeni. 2021;14 (2):7–8. Russian.
28. Sinichkin AA. Tochki opory v prinyatii resheniya o naznachenii genno-inzhenernykh biologicheskikh preparatov patsiyentam s psoriaticheskim artritom. Effektivnaya farmakoterapiya. 2019; 15(6): 46–50. Russian.
29. Yurchenko AV, Taube AA, Shubnikova YeV, et al. Izucheniye potentsiala rossiyskogo rynka lekarstvennykh preparatov na osnove monoklonal'nykh antitel. Farmakoekonomika: teoriya i praktika. 2022;10(3): 5–11. DOI: 10.30809/phe.3.2022.1. Russian.
30. Sokolova VD, Sableva NA, Mladov VV, Tolkacheva DG. Effektivnost' targetnykh lekarstvennykh preparatov v terapii vzroslykh patsiyentov so srednetyazhelym i tyazhelym vul'garnym psoriazom v Rossiyskoy Federatsii: obnovleniye sistematicheskogo obzora. Farmakoekonomika. Sovremennaya farmakoekonomika i farmakoepidemiologiya. 2022; 15(1): 131–144. DOI: 10.17749/2070-4909/farmakoekonomika.2022.128. Russian.

Литература

1. Клинические рекомендации «Псориаз». Режим доступа: [Электронный ресурс]. URL: http://cr.rosminzdrav.ru/#!/recomend/866 (дата обращения 15.12.2023 г.)
2. Федотова В. П., Дюдюна А. Д., Степаненко В. И. Дерматовенерология. Учебное пособие для врачей и врачей-интернов. Изд. 2-е. рус. Днепропетровск — Киев. Изд-во «Свидлер А. Л.». 2011; 652 с.
3. Всемирный доклад о проблеме псориаза. Режим доступа: [Электронный ресурс]. URL: https://apps.who.int/iris/handle/10665/204417 (дата обращения 15.12.2023 г.)
4. Кубанов А. А., Богданова Е. В. «Эпидемиология псориаза среди населения старше трудоспособного возраста и объемы оказываемой специализированной медицинской помощи больным псориазом в Российской Федерации в 2010–2019 гг.». Вестник дерматологии и венерологии. 2020; 96(5): 07–18. DOI: 10.25208/vdv1171-2020-96-5-07-18
5. Mease PJ, Gladman DD, Papp KA, et al. Prevalence of rheumatologist-diagnosed psoriatic arthritis in patients with psoriasis in European/North American dermatology clinics. Journal of the American Academy of Dermatology. 2013; 69(5): 729–735.
6. Армстронг А. В., Рид С. Патофизиология, клиническая картина и лечение псориаза: обзор. Джей Ам Мед Ассоц. 2020; 323(19): 1945–1960.
7. Рамик Л., Сатор П. Местное лечение вульгарного псориаза. JDDG: Журнал Deutschen Dermatologischen Gesellschaft. 2023; 21: 631–642. DOI: 10.1111/ddg.15042
8. Герасимов В. Б., Хохлов А. Л., Карпов О. И. Фармакоэкономика и фармакоэпидемиология — практика приемлемых решений. 2005; 1: 14–15.
9. Ohata C, Ohyama B, Katayama E, et al. Real-world efficacy and safety of interleukin-17 inhibitors for psoriasis: a single-center experience. J Dermatol. 2020; 47(4):405–408. DOI: 10.1111/1346-8138.15247.
10. Hayashida K, Murakami G, Matsuda S, et al. History and profile of diagnosis procedure combination (DPC): development of a real data collection system for acute inpatient care in Japan. J Epidemiol. 2021;31(1):1–11. DOI: 10.2188/jea. JE20200288.
11. Довжанский С. И., Утц С. Р. Псориаз или псориатическая болезнь в 2-х ч. Саратов. Изд-во Саратовск. ун-та. 1992;(1): 176 с.; 1992;(1): 96.
12. Зильберберг Н. В., Кащеева Я. В., Киселева Н. В., Кохан М. М. Опыт терапии больных псориазом препаратом метотрексат в форме подкожных и внутримышечных инъекций. Режим доступа: [Электронный ресурс]. URL: https://www.lvrach.ru/2021/11/15438141(дата обращения 15.12.2023 г.)
13. Наст А., Альтенбург А., Огюстен М. и др. Немецкое руководство S3 по лечению обыкновенного псориаза, адаптированное из EuroGuiDerm. Цели лечения и рекомендации по лечению. J Dtsch Дерматол Гес. 2021;19(6):934–1150.
14. Лангенбрух А., Радтке М. А., Якоби А. и др. Качество лечения псориаза в Германии: результаты национального исследования здравоохранения «PsoHealth3». Арка Дерматол Рес. 2016;308(6):401–408.
15. Галлямова Ю. А., Асоскова А. В. Метотрексат в дерматологии: от теории к практике. Лечащий Врач. 2021; 5 (24): 46–51.
16. Nash P, Coates LC, Fleischmann R, et al. Efficacy of tofacitinib for the treatmentof psoriatic arthritis: Pooled analysis of two phase 3 studies. Rheumatol Ther. 2018;5(2):567–82.
17. Инструкция по медицинскому применению препарата Скайризи. Режим доступа: [Электронный ресурс]. URL: http://grls.rosminzdrav.ru/Default доступ 01.07.2023. (дата обращения 15.12.2023 г.)
18. Инструкция по медицинскому применению препарата Гуселькумаб. Режим доступа: [Электронный ресурс]. URL: http://grls.rosminzdrav.ru/Default доступ 01.07.2023 (дата обращения 15.12.2023 г.)
19. Инструкция по медицинскому применению препарата Секукинумаб. Режим доступа: [Электронный ресурс]. URL: http://grls.rosminzdrav.ru/Default доступ 01.07.2023. (дата обращения 15.12.2023 г.)
20. Инструкция по медицинскому применению препарата Нетакимаб. Режим доступа: [Электронный ресурс]. URL: http://grls.rosminzdrav.ru/Default доступ 01.07.2023. (дата обращения 15.12.2023 г.)

21. Инструкция по медицинскому применению препарата Иксекизумаб. Режим доступа: [Электронный ресурс]. URL: http://grls.rosminzdrav.ru/Default доступ 01.07.2023. (дата обращения 15.12.2023 г.)
22. Инструкция по медицинскому применению препарата Адалимумаб: Режим доступа: [Электронный ресурс]. URL: http://grls.rosminzdrav.ru/Default доступ 01.07.2023. (дата обращения 15.12.2023 г.)
23. Perrone V, Losi S, Filippi E, et al. Analysis of the pharmacoutilization of biological drugs in psoriatic arthritis patients: a real-world retrospective study among an Italian population. Rheumatol Ther. 2022;9(3):875–890. DOI: 10.1007/s40744-022-00440-1.
24. Colombo D, Bianchi L, Fabbrocini G, et al. Real-world evidence of biologic treatments in moderate-severe psoriasis in Italy: results of the CANOVA study. Dermatol Ther. 2022;35(1):15166.
25. Xu C, Teeple A, Wu B, et al. Treatment adherence and persistence of seven commonly prescribed biologics for moderate to severe psoriasis and psoriatic arthritis in a U.S. commercially insured population. J Dermatolog Treat. 2022; 33(4): 2270–2277. DOI: 10.1080/09546634.2021.1950600
26. Толкачева Д. Г., Соколова В. Д., Младов В. В. Эффективность и безопасность таргетных лекарственных препаратов в терапии взрослых пациентов со среднетяжелым и тяжелым вульгарным псориазом в РФ. Медицинские технологии. Оценка и выбор. 2019; 4:76–86.
27. Рудакова А. В., Толкачева Д. Г., Соколова В. Д. Фармакоэкономические аспекты терапии псориатического артрита среднетяжелой и тяжелой степени. 2021;14 (2):7–8.
28. Синичкин А. А. Точки опоры в принятии решения о назначении генно-инженерных биологических препаратов пациентам с псориатическим артритом. Эффективная фармакотерапия. 2019; 15(6): 46–50.
29. Юрченко А. В., Таубэ А. А., Шубникова Е. В. и др. Изучение потенциала российского рынка лекарственных препаратов на основе моноклональных антител. Фармакоэкономика: теория и практика. 2022;10(3): 5–11. DOI: 10.30809/phe.3.2022.1.
30. Соколова В. Д., Саблева Н. А., Младов В. В., Толкачева Д. Г. Эффективность таргетных лекарственных препаратов в терапии взрослых пациентов со среднетяжелым и тяжелым вульгарным псориазом в Российской Федерации: обновление систематического обзора. Фармакоэкономика. Современная фармакоэкономика и фармакоэпидемиология. 2022; 15(1): 131–144. DOI: 10.17749/2070-4909/farmakoekonomika.2022.128.

ETHICAL ASPECTS, SAFETY ISSUES OF CARDIAC SURGERY AND PREDICTION OF ADVERSE EVENTS

Shereshneva MV[1] ✉, Ilyin MV[1,2]

[1] Regional Clinical Hospital, Yaroslavl, Russia

[2] Yaroslavl State Medical University, Yaroslavl, Russia

In cardiac surgery, patient's awareness and consent to surgery are problematic as due to the lack of previous medical background a patient can't understand the processes occurring in the body and effects of exposure on them. Thus, provision of sufficient information by a doctor is a part of safe surgical strategy. An open randomized prospective trial involving 89 patients with stable coronary artery disease (CAD) was conducted. High rate of blood oxidation is believed to be an independent predictor of cognitive dysfunction development during the early postoperative period of coronary artery bypass grafting (CABG). Determination of blood oxidation rate is a tool of risk management during cardiac surgery starting from the stage of preoperative preparation, which is optimal to implement a safe strategy, including psychological and drug-induced support of the patient aimed at prevention of cognitive disturbances.

Key words: coronary artery disease, cardiac surgery, safety, oxidative stress

Author contribution: Shereshneva MV - review of actual Russian and foreign literature related to the examined issue, identification of the study subject, determination of the goal and objectives, laboratory examination of induced blood oxidation values, mathematical and statistical data processing, making conclusions; Ilyin MV — development of study program, formulation of the study subject, determination of goal and objectives, mathematical and statistical data processing, making conclusions.

Compliance with ethical standards: the study underwent ethical expertise and was approved by the Ethics Committee of the Yaroslavl State Medical University of the Ministry of Health of Russia. Prior to inclusion, the patients were explained the study goals and objectives in detail, and a voluntary informed consent was obtained.

✉ **Correspondence should be addressed:** Marina V. Shereshneva
Revolutsionnaya Str., bld. 5, Yaroslavl 150000, Russia; m.shereshneva@yandex.ru

Received: 26.11.2023 **Accepted:** 21.01.2024 **Published online:** 29.02.2024

DOI: 10.24075/medet.2023.034

ЭТИЧЕСКИЕ АСПЕКТЫ, ПРОБЛЕМЫ БЕЗОПАСНОСТИ КАРДИОХИРУРГИЧЕСКОГО ВМЕШАТЕЛЬСТВА И ПРЕДИКЦИЯ НЕБЛАГОПРИЯТНЫХ СОБЫТИЙ

М. В. Шерешнева[1] ✉, М. В. Ильин[1,2]

[1] Областная клиническая больница, г. Ярославль, Россия

[2] Ярославский государственный медицинский университет, г. Ярославль, Россия

В области кардиохирургии аспект информированности и согласия пациента на проведение операции представляется проблематичным, ведь не имеющему медицинских знаний больному трудно представить себе процессы, происходящие в организме или последствия воздействия на эти процессы. В связи с этим предоставление врачом всей полноты информации является частью безопасной стратегии хирургического вмешательства. Проведено открытое нерандомизированное проспективное исследование в группе, состоящей из 89 больных стабильной ишемической болезнью сердца. Установлено, что высокая скорость окисления крови является независимым предиктором развития когнитивной дисфункции в раннем послеоперационном периоде при проведении шунтирования коронарных артерий. Определение скорости окисления крови является одним из инструментов управления рисками при выполнении кардиохирургического вмешательства, начиная с этапа предоперационной подготовки, который представляется оптимальным для реализации безопасной стратегии, включая психологическую и медикаментозную поддержку пациента, направленную на предотвращение развития когнитивных нарушений.

Ключевые слова: ишемическая болезнь сердца, кардиохирургия, безопасность, окислительный стресс

Вклад авторов: М. В. Шерешнева— обзор актуальной отечественной и зарубежной литературы по изучаемой проблеме, формулирование темы исследования, определение его цели и задач, лабораторное исследование показателей индуцированного окисления крови, математико-статистическая обработка данных, формулирование выводов; М. В. Ильин— разработка программы исследования, формулирование темы исследования, определение цели и задач исследования, математико-статистическая обработка данных, формулирование выводов.

Соблюдение этических стандартов: исследование прошло этическую экспертизу и было утверждено Этическим комитетом ФГБОУ ВО ЯГМУ Минздрава России. До включения в исследование пациентам были подробно разъяснены его цели и задачи, было получено добровольное информированное согласие.

✉ **Для корреспонденции:** Марина Владимировна Шерешнева
ул. Революционная, д. 5, г. Ярославль, 150000, Россия; m.shereshneva@yandex.ru

Статья поступила: 26.11.2023 **Статья принята к печати:** 21.01.2024 **Опубликована онлайн:** 29.02.2024

DOI: 10.24075/medet.2023.034

Cardiac surgery is a serious step of a patient's life. Its outcomes mainly depend on a psychological attitude, awareness and behavior at an early stage of rehabilitation. There are known associations between psychological factors and the intensity of pain during the postoperative period, quality of life, and surgical outcomes [1]. Although compliance with the rules of medical ethics has always been part of cardiac surgery practice, ethical suggestions have recently become its essential component. Informed consent, conflict of interests, professional self-regulation, and many other issues increasingly attract attention of cardiologists and cardiac surgeons [2].

In exceptional cases a doctor has to take decisions, which contradict the principles of classical medical ethics, due to high achievements of biological and medical science and introduction of novel medical technologies. Great attention to personality rights, including the right of a patient, has provided

new insights into relationship between a doctor and a patient, which became a prerequisite for occurrence and development of biomedical ethics, which is a combination of biological knowledge and human values [3].

One of the key points determining the course of post-operative period and prognosis include compliance to treatment and the patient's awareness of the risk of possible complications. In this regard, discussing the issues of drug support and determining the risk of surgical intervention at the stage of preparation to surgery will allow him to decide on consent to the operation, and the correction of psycho-emotional stress will provide an opportunity to manage the psycho-emotional state, increase adherence and improve the prognosis [4].

Previous studies show a significant decrease in severity of anxious, hypochondriacal and sensitive types of attitude towards the disease, as well as a decrease in the severity of unproductive coping strategies and a decrease in the level of depression in patients after coronary artery bypass surgery against the background of perioperative psychological support and an early start of physical rehabilitation [5]. According to available data, it is the predominance of productive copying strategies, that is associated with better adherence to therapy in patients with CAD undergoing coronary artery bypass surgery, while unproductive coping is typical for patients with low compliance [6].

Nowadays the number of non-urgent interventions for myocardial revascularization in patients with CAD is increasingly growing. Despite improvements in the technique of performing coronary artery bypass grafting and an increase in the number of operations without cardiopulmonary bypass, there remains a high risk of development of perioperative complications [7]. Prediction and quantitative assessment of adverse events probability during coronary artery bypass grafting becomes an important element of the patient's psychological preparation for surgery.

The purpose of the study is to determine the predictors of unfavorable events during CABG in the context of increasing the patient's psychological readiness for surgery.

PATIENTS AND METHODS

The study was conducted at the Yaroslavl Regional Clinical Hospital (the city of Yaroslavl). The work was included into the program of scientific studies of the Yaroslavl State Medical University of the Ministry of Health of Russia and went through ethical review procedures. 89 patients with stable CAD aged 58.1 ± 8.3, including 70 men aged 57.8 ± 8.2 years and 19 women aged 63.9 ± 6.9 years were examined. The control group consisted of 24 relatively healthy donors, including 9 (37.5%) men and 15 (62.5%) women aged 50.0 ± 9.0 years. CAD was confirmed by the results of a clinical examination, stress tests and coronary angiography data. Medical management complied with up-to-date clinical recommendations.

Induced blood oxidation parameters were assessed using a YSI 5300 biological oxygen monitor (Yellow Springs Instrument Company, YSI Inc., USA). Free radical oxidation of blood components was induced by the water-soluble inducer AAPH (2,2'-azobis (2-amidino-propane) dihydrochloride). The rate of blood oxidation (V_{ox}), 10^{-8} mol/L·s; time of initiation period (T), min; initial rate of blood oxidation (V_{init}), 10^{-8} mol/L·s; maximum rate of blood oxidation (V_{max}), 10^{-8} mol/L·s; terminal rate of oxidation V_{term}, 10^{-8} mol/L·s; and coefficient of oxidative activity (K_A), % were determined from the slope of the oxygen concentration curve in the sample;

The Mini Mental State Examination (MMSE) assay (Folstein M. F. et al, 1975) was used to screen and assess the severity of post-operative cognitive dysfunction. Cognitive functions were assessed after the effects of anesthesia had subsided.

Statistical analysis of the data was performed using STATISTICA 10.0 (StatSoft Inc., США). The normality of the distribution of variables was checked using the Kolmogorov-Smirnov tests with the Lilliefors and Shapiro-Wilk correction. To study the relationship between two characteristics, Spearman correlation analysis was used. The study of the type of dependence of a trait on one or more other traits was carried out on the basis of logistic regression analysis. The critical value of statistical significance level was 5.0%.

STUDY RESULTS

The results of comparative analysis of induced blood oxidation parameters in patients with CAD are shown in table 1.

Patients with stable CAD had higher values of blood oxidation rate (2.07 > 1.9; $p = 0.049$), a shorter initiation period (0.97 < 1.91; $p = 0.001$), a higher initial rate of blood oxidation (3.29 > 2.11; $p = 0.0001$), a higher maximum rate of blood oxidation (3.5 > 2.54; $p = 0.001$), and a higher coefficient of oxidative activity (40.0 > 5.89, $p = 0.0001$) comparing to the control group.

The results of the analysis of the influence of induced blood oxidation rate values on the development of cognitive dysfunction in the early postoperative period are presented in Table 2.

Table 1. Comparative analysis of induced blood oxidation parameters in patients with CAD

Attribute	Control	CAD	p
Blood oxidation rate (V_{ox}), 10^{-8} mol/l·s	1.90 (1.7; 2.2)	2.07 (1.8; 2.3)	**0.049**
Time of initiation period (*T*), min	1.91 (1.3; 2.5)	0.97 (0.67; 1.34)	**0.001**
Initial oxidation rate (V_{init}), 10^{-8} mol/l·s	2.11 (1.6; 2.9)	3.29 (2.5; 4.83)	**0.0001**
Maximum oxidation rate (V_{max}), 10^{-8} mol/L·s	2.54 (2.1; 3.1)	3.5 (2.76; 4.83)	**0.001**
Ultimate oxidation rate V_{term}, 10^{-8} mol/L·s	1.86 (1.6; 2.2)	2.03 (1.76; 2.33)	0.28
Oxidation activity coefficient (K_A), %	5.89 (–11.0; 22.7)	40 (15.65; 55.5)	**0.0001**

Table 2. Influence of blood oxidation rate (V_{ox}) on development of cognitive dysfunction in patients with CAD during the postoperative period

	Multiple — R	Multiple — R2	Adjusted — R2	SS — Model	df — Model	MS — Model	F	*p*
Cognitive dysfunction	0.34	0.12	0.10	0.33	1	0.33	8.80	**0.004**

Logistic regression analysis proved the influence of blood oxidation rate on the development of cognitive dysfunction in the postoperative period of CABG (p=0.004). Patients with high blood oxidation rate values represent a risk group for the development of cognitive dysfunction during coronary artery bypass grafting.

DISCUSSION OF RESULTS

Oxidative stress is a component of the neuroinflammatory process, which is a common link in neurodegenerative diseases [8]. A number of large studies have proved the existence of a persistent relationship between oxidative stress and the development of neurodegenerative diseases, primarily Alzheimer's disease [9, 10]. Patients with depressive disorders have also been found to exhibit compromised oxidative status [11]. Low plasma antioxidant activity is associated with a larger focal area in patients with ischemic stroke [12]. Low plasma antioxidant activity is an independent predictor of delirium development in the postoperative period of coronary artery bypass grafting [13].

Current studies focus on the pathogenesis of neurodegenerative diseases associated with the development of dementia, such as Alzheimer's disease or Parkinson's disease. The mechanism underlying transient neurocognitive disorders after surgical interventions is poorly understood. Oxidative stress and disturbances of autophagy processes that occur during cardiac surgery as part of the ischemia-reperfusion phenomenon are integral pathogenetic links of systemic inflammation, which, probably, is in close connection with the development of neurocognitive disorders in the postoperative period. Together with the developing mitochondrial dysfunction, pathologic protein aggregation, impaired neurotransmitter metabolism, and inflammation, this leads to neuronal death [14].

The brain is extremely sensitive to oxidative stress, mainly due to high metabolic activity and relatively weak endogenous antioxidant defenses. Another important fact is the effect of oxidative stress on the Ca^{2+} current that control bidirectional synaptic transmission. The intracellular Ca^{2+} accumulation can indirectly lead to inhibition of mitochondrial respiration and the accumulation of free radicals that damage cellular structures [15].

Thus, transitory disturbances of oxidative status during cardiac surgery lead to temporary neurocognitive disturbances by acting on the nervous system which is sensitive to homeostatic disruption. In this case, the effect of oxidative stress is not long enough to obtain a stable degenerative process.

Thus, transient disturbances in oxidative status observed during cardiac surgery, affecting the nervous system, which is sensitive to homeostasis disturbances, lead to temporary neurocognitive disorders. In this case, the effect of oxidative stress is not long enough for a persistent degenerative process to occur.

CONCLUSIONS

High blood oxidation rate is an independent predictor of the development of cognitive dysfunction in the early postoperative period during coronary artery bypass grafting.

Determination of blood oxidation rate is one of the tools for risk management during cardiac surgery, starting from the preoperative preparation stage, which seems to be optimal for the implementation of a safe strategy, including psychological and medication support of the patient aimed at preventing the development of cognitive impairment.

The emergence of new medical technologies contributes to the development of ethical thought in the world, when the original main moral principle of medicine, the preservation of human life, is joined by others related to the right of a person to dispose of this life, as well as to have full information not only about the state of health, but also about the prognosis of the disease, which, among other things, is related to the safety of cardiac surgery and the prediction of the development of adverse events.

References

1. Solodukhin AV, Trubnikova OA, Yanitskiy MS, Seryy AV, Barbarash OL. Kliniko-psikhologicheskaya kharakteristika patsiyentov s IBS pered podgotovkoy k koronarnomu shuntirovaniyu v zavisimosti ot ikh psikhoemotsional'nogo statusa. Lechashchiy vrach. 2017; 11: 76–79. Russian.
2. Kavarana MN, Sade RM. Ethical issues in cardiac surgery. Future Cardiol. 2012; 8(3): 451–65.
3. Mzhavanadze ND. Sotsial'no-psikhologicheskiye aspekty professional'noy deyatel'nosti serdechno-sosudistogo khirurga. Lichnost' v menyayushchemsya mire: zdorov'ye, adaptatsiya, razvitiye. 2015; № 3(10): 53–58. Russian.
4. Argunova YuA, Barbarash OL. Optimizatsiya podgotovki patsiyenta k kardiokhirurgicheskomu vmeshatel'stvu. Kardiologiya i serdechno-sosudistaya khirurgiya. 2023; 2(16): 171–177. Russian.
5. Taran IN, Solodukhin AV, Argunova YuA, Pomeshkina SA, Barbarash OL. Funktsional'nyy i psikhologicheskiy status patsiyentov posle koronarnogo shuntirovaniya: effekty ranney reabilitatsii s aerobnymi fizicheskimi nagruzkami i perioperatsionnogo psikhologicheskogo soprovozhdeniya. Kardiologiya i serdechno-sosudistaya khirurgiya. 2021; 14(3): 164–170. Russian.
6. Pomeshkina SA, Bezzubova VA, Solodukhin AV, Seryy AV, Ardashova NYu. Svyaz' priverzhennosti k terapii s pokazatelyami psikhologicheskogo statusa patsiyentov, perenesshikh aortokoronarnoye shuntirovaniye. Doktor.Ru. 2017; 134(5): 36–41. Russian.
7. Bubnova MG, Aronov DM, Sprikut AA, Stankevich DI, Poddubskaya YeA, Persiyanova-Dubrova AL. Preabilitatsiya kak vazhnyy etap pered kardiokhirurgicheskimi vmeshatel'stvami. Kardiovaskulyarnaya terapiya i profilaktika. 2021; 20 (6): 99–106. Russian.
8. Webers A, Heneka MT, Gleeson PA. The role of innate immune responses and neuroinflammation in amyloid accumulation and progression of Alzheimer's disease. Immunology and cell biology. 2020; 98: 28–41.
9. Butterfield, DA, Halliwell B. Oxidative stress, dysfunctional glucose metabolism and Alzheimer disease. Nature reviews. Neuroscience. 2019; 20(3): 148–160.
10. Song T, Song X, Zhu C, et al. Mitochondrial dysfunction, oxidative stress, neuroinflammation, and metabolic alterations in the progression of Alzheimer's disease: A meta-analysis of in vivo magnetic resonance spectroscopy studies. Ageing research reviews. 2021; 72: 101503.
11. Black CN, Bot M, Scheffer PG, et al. Is depression associated with increased oxidative stress? A systematic review and meta-analysis. Psychoneuroendocrinology. 2015; 51: 164–175.
12. Leinonen JS, Ahonen JP, Lönnrot K, et al. Low plasma antioxidant activity is associated with high lesion volume and neurological impairment in stroke Stroke. 2000; 31(1): 33–39.
13. Kaźmierski J, Miler P, Pawlak A, et al. Oxidative stress and soluble receptor for advanced glycation end-products play a role in the pathophysiology of delirium after cardiac surgery. Scientific reports. 2021; 11(1): 23646.
14. Konovalova J, Gerasymchuk D, Parkkinen I, et al. Interplay between MicroRNAs and Oxidative Stress in Neurodegenerative Diseases. International journal of molecular sciences. 2019; 20(23): 6055.
15. Cobley JN, Fiorello ML, Bailey DM. 13 reasons why the brain is susceptible to oxidative stress. Redox Biology. 2018; 15: 490–503.

Литература

1. Солодухин А. В., Трубникова О. А., Яницкий М. С., Серый А. В., Барбараш О. Л. Клинико-психологическая характеристика пациентов с ИБС перед подготовкой к коронарному шунтированию в зависимости от их психоэмоционального статуса. Лечащий врач. 2017; 11: 76–79.
2. Kavarana MN, Sade RM. Ethical issues in cardiac surgery. Future Cardiol. 2012; 8(3): 451–65.
3. Мжаванадзе Н. Д. Социально-психологические аспекты профессиональной деятельности сердечно-сосудистого хирурга. Личность в меняющемся мире: здоровье, адаптация, развитие. 2015; № 3(10): 53–58.
4. Аргунова Ю. А., Барбараш О. Л. Оптимизация подготовки пациента к кардиохирургическому вмешательству. Кардиология и сердечно-сосудистая хирургия. 2023; 2(16): 171–177.
5. Таран И. Н., Солодухин А. В., Аргунова Ю. А., Помешкина С. А., Барбараш О. Л. Функциональный и психологический статус пациентов после коронарного шунтирования: эффекты ранней реабилитации с аэробными физическими нагрузками и периоперационного психологического сопровождения. Кардиология и сердечно-сосудистая хирургия. 2021; 14(3): 164–170.
6. Помешкина С. А., Беззубова В. А., Солодухин А. В., Серый А. В., Ардашова Н. Ю. Связь приверженности к терапии с показателями психологического статуса пациентов, перенесших аортокоронарное шунтирование. Доктор.Ру. 2017; 134(5): 36–41.
7. Бубнова М. Г., Аронов Д. М., Сприкут А. А., Станкевич Д. И., Поддубская Е. А., Персиянова-Дуброва А. Л. Преабилитация как важный этап перед кардиохирургическими вмешательствами. Кардиоваскулярная терапия и профилактика. 2021; 20 (6): 99–106.
8. Webers A, Heneka MT, Gleeson PA. The role of innate immune responses and neuroinflammation in amyloid accumulation and progression of Alzheimer's disease. J. Immunology and cell biology. 2020; 98: 28–41.
9. Butterfield DA, Halliwell B. Oxidative stress, dysfunctional glucose metabolism and Alzheimer disease. J. Nature reviews. Neuroscience. 2019; 20(3): 148–160.
10. Song T, Song X, Zhu C, et al. Mitochondrial dysfunction, oxidative stress, neuroinflammation, and metabolic alterations in the progression of Alzheimer's disease: A meta-analysis of in vivo magnetic resonance spectroscopy studies. J. Ageing research reviews. 2021; 72: 101503.
11. Black CN, Bot M, Scheffer PG, et al. Is depression associated with increased oxidative stress? A systematic review and meta-analysis. J. Psychoneuroendocrinology. 2015; 51: 164–175.
12. Leinonen JS, Ahonen JP, Lönnrot K, et al. Low plasma antioxidant activity is associated with high lesion volume and neurological impairment in stroke. J. Stroke. 2000; 31(1): 33–39.
13. Kaźmierski J, Miler P, Pawlak A, et al. Oxidative stress and soluble receptor for advanced glycation end-products play a role in the pathophysiology of delirium after cardiac surgery. J. Scientific reports. 2021; 11(1): 23646.
14. Konovalova J, Gerasymchuk D, Parkkinen I, et al. Interplay between MicroRNAs and Oxidative Stress in Neurodegenerative Diseases. J. International journal of molecular sciences. 2019; 20(23): 6055.
15. Cobley JN, Fiorello ML, Bailey DM. 13 reasons why the brain is susceptible to oxidative stress. Redox Biology. 2018; 15: 490–503.

BIOETHICS, LAW AND INTERESTS OF FUTURE GENERATIONS — SOME PRACTICAL AREAS OF COMMON INTEREST

Kopeikin PA ✉

Yaroslavl State Medical University, Yaroslavl, Russia

The article defines the term 'bioethics' taking into account the common regulatory act, shows the interrelation between bioethical and legal regulations, and defines the mechanisms that enhance and improve effectiveness of ethical standards by turning them into legal regulations. Basic regulatory legal acts such as laws and subordinate acts in health regulation are reviewed and analyzed for the presence of an ethical constituent. Critical areas in the regulatory acts are specified; certain ways of their ethical transformation are mentioned. Insufficient ethical substantiation of regulatory provisions in the body of legislation and lack of universal declarative regulations are found. The role of a new subject of bioethics and law (future generations), which significantly expands the area of ethical issues, including applied medical sciences, has been denoted. The conflict between modern ethics and interests of future generations can be a complex issue and should be solved immediately on a constant basis. Ethical and legal principles of future generations — precaution and non-regression — were introduced. It is indicated that the standards of ethical and legal regulation of interests of future generations should be developed.

Key words: bioethics, law, health care, legislation, clinical research, ethics, principles of law, legal personality, future generations, genetics

✉ **Correspondence should be addressed:** Pavel A. Kopeikin
Revolutsionnay Str., 5, Yaroslavl, 150000, Russia; medpravo80@mail.ru

Received: 29.01.2024 **Accepted:** 25.02.2024 **Published online:** 13.03.2024

DOI: 10.24075/medet.2024.002

БИОЭТИКА, ПРАВО И ИНТЕРЕСЫ БУДУЩИХ ПОКОЛЕНИЙ — НЕКОТОРЫЕ ПРАКТИЧЕСКИЕ ТОЧКИ СОПРИКОСНОВЕНИЯ

П. А. Копейкин ✉

Ярославский государственный медицинский университет, Ярославль, Россия

В статье дано определение биоэтики исходя из общепризнанного нормативного акта, показана взаимосвязь биоэтических и правовых норм, определены механизмы усиления и улучшения эффективности этических норм путем их превращения в правовые нормы, т.е. легализации. Разобраны основные нормативно-правовые акты — законы и подзаконные акты в сфере охраны здоровья с анализом на присутствие этической составляющей. Обозначены уязвимые места в нормативных актах и указаны некоторые пути их этического преобразования. Выявлены недостаточное этическое обоснование нормативных положений в общем массиве законодательства и отсутствие полноценных декларативных норм. Обозначена роль нового субъекта биоэтики и права — «будущих поколений», который значительно расширяет круг этических вопросов, в том числе и в прикладных медицинских науках. Конфликт между этикой современности и интересами будущих поколений может представлять собой сложную проблему и должен быть решаем уже сейчас, причем на постоянной основе. Введены этико-правовые принципы будущих поколений — предосторожности и нерегрессности. Указана необходимость разработки норм этического и правового регулирования интересов будущих поколений.

Ключевые слова: биоэтика, право, охрана здоровья, законодательство, клинические исследования, этика, принципы права, правосубъектность, будущие поколения, генетика

✉ **Для корреспонденции:** Павел Александрович Копейкин
ул. Революционная, д. 5, г. Ярославль, 150000, Россия; medpravo80@mail.ru

Статья поступила: 29.01.2024 **Статья принята к печати:** 25.02.2024 **Опубликована онлайн:** 13.03.2024

DOI: 10.24075/medet.2024.002

Bioethics — what is it? Considering it from the point of view of the science of values, it seems to us that bioethics is, first of all, a set of certain values and procedures for applying these values in practice. Asking the question of finding a definition of the concept of bioethics, let us turn to the internationally recognized act — the "Universal Declaration on Bioethics and Human Rights of UNESCO" of 2005 [1], which states that the scope of the declaration: "Ethical issues relating to medicine, life sciences and related them technologies in relation to humans, taking into account their social, legal and environmental aspects" [1]. Actually, this is a brief definition of bioethics. What is important to emphasize here is an indication of the mandatory legal aspect of bioethics. Thus, the answers to ethical questions and dilemmas are also found in the legal system, and even more than that, the set of values of bioethics is contained in the rules of law or should, if possible, be partially contained in them. The legal system is thus the source in which we must seek answers to most of the bioethical questions that interest us. Moreover, we must never forget that bioethics is a practical institution and social relations that are included in the range of its interests are simply obliged to be regulated by the state due to their exceptional importance for society, and such a regulator is the law — the rules of law. Another important conclusion that follows from the above is that any value of bioethics, any of its provisions should not contradict legal norms, even without being included in the law.

Is the above definition of the concept "bioethics" complete? It seems to us that the subjects and objects of bioethics lie not only in modernity, in the present time, and it is impossible to develop concepts of bioethics only in relation to the current or slightly distant moment. What standards of bioethics will be in 50–100 years we need to think now and anticipate possible future relations in modern standards, especially in the field of new technologies, for example, in operations with the genome, artificial intelligence in healthcare. Only then will our behavior be responsible. Thus, a new subject of bioethics appears on the

arena — future generations, posing even more questions than real relationships.

"We, the multinational people of the Russian Federation, based on responsibility for our Motherland before present and future generations, accept the Constitution of the Russian Federation," says our Constitution at its very beginning, showing the exceptional importance of the institution of future generations [2]. We can even say more — a new conflict field has emerged between the ethics of the modern generation and the ethics of future generations. But any concept will remain just an optional guide to action and an ephemeral philosophical construct without reliable anchoring. In what ways can bioethical rules be established that protect future generations? The best and most reliable way is through law. But the law is vast, and the best place to start is with its most basic and reliable sources — principles. The principles of the rights of future generations are the most reliable mechanism. Let's try to formulate them. The first is the precautionary principle. Its meaning is that as a result of the decisions made, we must make sure whether the situation of all interested parties is not worsening, including projection into the future. The second is the principle of non-regression. He says that the already achieved level of protection cannot be reduced; new bioethical norms should not worsen the situation of subjects in comparison with existing ones. But this is not always possible and it is also necessary to provide in some cases the possibility of reducing the level of protection with an adequate analysis of the balance of risks and in order to protect other fundamental rights, but the principle of proportionality must be taken into account and objective evidence of the need for such a step must be applied. Initially, the international doctrine of the rights of future generations considered only issues of ecology and environmental protection, but at the current level of development of social relations, other bioethical issues also become important for us, for example, in the field of genetics — these are the rights of unborn descendants of persons subjected to gene therapy or other modification genome. Regardless of the degree and line of kinship in the ascending and descending line, relatives have rights to the common part of the genetic material that unites them to the extent that their interests may be affected by the disclosure of this genetic information or in the event of its modification transmitted by inheritance. This is a new type of personal genetic data, which defines a new vast group of relationships, and which is not yet clear how and to what extent to regulate. This will require, it seems to us, a precise definition and consolidation in legislation of different degrees of kinship from the standpoint of the legal circulation of genetic data; until now this has not been necessary. So today the legislation — Article 14 of the Family Code of the Russian Federation speaks only about close relatives [3]. A more thorough study of the degrees and forms of kinship (direct and collateral lines of kinship) and the introduction of appropriate changes to both the Family and Civil Codes and newly created regulations is required. Thus, we can talk about a new direction — ethics and the law of kinship relations from the perspective of the genetic interests of present and future generations.

Regarding the issue of creating an institutional system for the protection of the rights of future generations, it is necessary to determine the bodies that may be included in it — this could be, for example, the Constitutional Court, the institution of the Commissioner for the Rights of Future Generations recognized in international law, the prosecutor's office, in the field of clinical research — this there may be ethics committees and other bodies.

Let us now consider some ethical aspects and issues related to the relationship between legal and ethical norms, as well as the need to regulate the rights of future generations. The basic law in the field of health protection — the Federal Law "On the Fundamentals of Protecting the Health of Citizens in the Russian Federation" [4] does not contain a definition of the concept of bioethics, but nevertheless the norms of Chapter 2, as fundamental for the entire law, reveal many of the values of bioethics. In by-laws, it should be noted that the concept of "bioethics" is extremely rare.

Therefore, the primary task is to supplement Article 2 of the law "On the fundamentals of protecting the health of citizens in the Russian Federation" with a definition of bioethics, which provides an interpretation of the basic concepts used in the field of health protection.

Next, we will dwell in more detail on the values of bioethics contained in the norms regulating most areas of health care. First of all, speaking about the main act — the Federal Law "On the fundamentals of protecting the health of citizens in the Russian Federation", we will emphasize that Chapter 2 is devoted to the basic principles of health protection. This is a very important chapter, and the principles are provisions that, despite the widespread misconception about their declarative nature, still act directly. Action directly means that they do not require additional reference to other individual norms (articles), but work independently and you can and even need to refer to them directly to defend your position — bioethical and legal. Separately, we can also highlight in this law the current, modern Article 96 [4], which deals with monitoring the safety of medical devices, and from the standpoint of the rights of future generations, it seems to us that it needs to be supplemented with the following content: "Monitoring the safety of medical devices must contain "implementation of precautions and consideration of possible adverse consequences in the future." It is also very important to imbue Chapter 2 of the same source with additional ethical content and to more fully reveal some of the values. For example, Article 6 of the above Federal Law: "Priority of the interests of the patient in the provision of medical care" can be clarified and stated in the following form: "The interests and well-being of the individual patient (person) must prevail over the interests of science or society" [4].

Some of the norms of bioethics that regulate the most important social relations, or rather, deviations from these bioethical norms, are enshrined in the Criminal Code in the form of crimes, therefore, criminal liability measures are provided for violation of these norms [5]. The array of criminal norms is, of course, gradually replenished with new elements as social relations become more complex. International law even attempts to develop the institution of criminal liability to future generations. Thus, it seems to us that we should soon expect the establishment of criminal liability for the unlawful use of genetic data, resulting in a violation of the interests or harm to the health of present and future generations; for concealing information about circumstances that pose a danger to the life or health of future generations; for violation of sanitary and epidemiological rules and regulations, resulting in a violation of the rights of future generations.

Bioethical values related to vulnerable communities and individuals, such as those suffering from mental and behavioral disorders, are very important. Therefore, the Law "On Psychiatric Care and Guarantees of the Rights of Citizens in its Provision" [6] is so urgent, the preamble of which states that the lack of proper legislative regulation of psychiatric care may be one of the reasons for its use for non-medical purposes, causing harm to human health dignity and rights of citizens, as

well as the international prestige of the state. Therefore, we can draw a very important conclusion — all bioethical norms governing relationships in the lives of any vulnerable categories must be fully and comprehensively enshrined in legal acts.

There is a Federal Law "On State Regulation in the Field of Genetic Engineering Activities" [7]. In the designated scope of the law, we see that it: "Regulates relations in the field of environmental management, environmental protection, environmental safety and human health protection that arise during the implementation of genetic engineering activities. The procedure for carrying out genetic engineering activities and applying its methods to a person, tissues and cells within his body, with the exception of gene diagnostics and gene therapy (gene therapy), is not subject to regulation by the Federal Law" [7]. Analyzing this act, we find a complete lack of ethical and legal regulation issues of gene diagnostics and gene therapy, which are stated in its subject. This gap needs to be corrected now. Moreover, these aspects also lie in the sphere of interests of future generations.

But the main directions of state regulation in the field of genetic engineering activities are, according to Article 5 of this law: "Improving human living conditions and protecting his health" [7], valuable here is an indication of the aspect of improving human living conditions, because this ethical provision is rare for legislative acts and, as it seems to us, can be used more and more often in legal norms.

Bioethical norms embedded in the rules of law, as we previously analyzed using the example of the norms of the Criminal Code, cannot work effectively without sanctions, but when the act does not yet constitute a crime, but only constitutes an offense, a misdemeanor, then the norms contained in the law come to the rescue. "Code of the Russian Federation on Administrative Offenses" [8]. For example, violations of legislation in the field of ensuring the sanitary and epidemiological well-being of the population may indirectly affect the rights of future generations and, accordingly, with the detailed development of the institution of rights of future generations, this act should be supplemented with new norms.

In some cases, reliable personal identification is necessary in practice. The procedure of mandatory genomic registration used for this is also difficult from an ethical point of view, especially with the issue of determining the grounds for it and, therefore, requires regulation by law. This law is called "On State Genomic Registration in the Russian Federation" [9]. The following subjects are subject to this registration: persons convicted and serving a sentence of imprisonment for committing crimes; unidentified persons whose biological material was seized during investigative actions; persons suspected of committing crimes, accused of committing crimes; Unidentified corpses are subject to mandatory state genomic registration. As we can see, this list represents vulnerable categories, and the law itself, in our opinion, therefore requires mandatory consolidation in it of ethical principles of working with both genetic data and subjects.

The next regulatory act is the law "On Biomedical Cell Products" [10], it regulates relations in this area. From the point of view of bioethics, we are interested in Article 3, which specifies the principles for carrying out activities in the field of circulation of biomedical cell products: "Voluntariness and gratuitousness of donation of biological material; inadmissibility of purchase and sale of biological material; the inadmissibility of creating a human embryo for the purpose of producing biomedical cell products" [10]. As we can see, these standards are entirely aimed at removing this area from commercial circulation to prevent, among other things, ethical abuses. It is extremely important, in our opinion, to extend these principles to the circulation of genetic material as well.

It is impossible not to mention the Federal Law "On the Donation of Blood and Its Components" dated July 20, 2012 N 125-FZ, Article 4 of which provides the basic ethical principles of donating blood and (or) its components: the safety of donor blood and its components; voluntary donation of blood and (or) its components; maintaining the health of the donor while performing the donor function; ensuring social support and respecting the rights of donors; encouragement and support of free donation of blood and (or) its components. We consider it appropriate to supplement these principles in the law with the principles of availability of blood and its components and guarantees of state support for the blood service.

Let us now turn to the lower level of regulatory legal acts, the so-called by-laws. As an example, we can cite the National Standard of the Russian Federation "Accessibility of urban infrastructure facilities for people with disabilities" [11]. Having reviewed it, we discovered that it lacks an explanatory ethical preamble, although its purpose is clear and understandable based on the title of the act. Ethical justification in documents related to vulnerable categories is mandatory, in our opinion, regardless of the level of the act.

There is also a Code of Professional Ethics for Physicians [12], it is fully saturated with bioethical norms and should be more widely used in practice, representing a version of soft law. It seems to us that in order to give it greater force, it is necessary to create local regulations on its basis as a collection of norms regulating the direct performance of labor duties.

And finally, professional standards for healthcare professionals contain ethical provisions regarding the observance of medical confidentiality, the doctor's oath, the principles of medical ethics and deontology in working with patients (legal representatives of patients), colleagues. For example, the Order of the Ministry of Labor and Social Protection of the Russian Federation "On approval of the professional standard "Physician (precinct general practitioner)" [13]. This legal framework has important practical significance when arguing for the imposition of possible disciplinary sanctions on medical workers.

Having analyzed the main national acts regulating the conduct of clinical trials and containing the values of bioethics: Order of the Ministry of Health of the Russian Federation of April 1, 2016 No. 200n "On approval of the rules of good clinical practice" [14]; Rules of good clinical practice of the Eurasian Economic Union (approved by the decision of the Council of the Eurasian Economic Commission of November 3, 2016 No. 79) [15]; National standard of the Russian Federation GOST R 52379–2005 "Good clinical practice", approved by order of the Federal Agency for Technical Regulation and Metrology dated September 27, 2005 No. 232-st [16]; GOST R ISO 14155–2014. "Clinical researches. Good clinical practice" [17], we come to the conclusion that provisions regarding the conduct of clinical trials are contained only at the level of by-laws. In our opinion, it is necessary to provide general provisions on clinical trials and ethical committees, as well as the principles of their functioning, either in the Federal Law "On the Fundamentals of Protecting the Health of Citizens in the Russian Federation" or in a special law, due to their great social significance.

Consolidating ethical standards in legal sources, as we have seen, presents a certain difficulty. As an example, let us cite one ethical obligation contained in a normative act. Thus, in accordance with Article 7, paragraph 21 of the Order of the Ministry of Health of the Russian Federation "On approval of the rules of good clinical practice" [14], the following requirement is

mandatory: “The clinical trial is carried out in accordance with the clinical trial protocol, which contains, among other things, a description ethical aspects of clinical research.” This is one of the few places in the entire scope of legislation where a clear indication is given of the mandatory application of ethical standards, which in itself is significant and should be the “gold” standard, an example for improving the law.

CONCLUSION

As we have also seen, bioethical norms are presented in legal acts at all levels, but not always fully; their more thorough elaboration and more complete consolidation are necessary, from this the normative acts only become better, clearer, more effective and more accessible. In connection with the emergence of a new subject of law — future generations, new ethical issues and the need to change and supplement legal norms arise.

Raising the question of the new scope of the concept of bioethics, we tried to briefly formulate the general principle: “Law and bioethics, inextricably and consistently, must think and act in the interests of future generations, while protecting the interests of the present.” Thus, our task for the future is to saturate existing and newly adopted legal acts with capacious ethical content — the values of bioethics, which in this way will gradually pass into the legal bed and become much stronger from this.

References

1. “The Constitution of the Russian Federation” (adopted by popular vote on 12/12/1993 with amendments approved during the all-Russian vote on 07/01/2020) Available from URL: http://pravo.gov.ru/proxy/ips/?docbody=&nd=102027595 (accessed 01.10.2024). Russian.
2. Universal Declaration on Bioethics and Human Rights. Adopted by a resolution of the General Conference of UNESCO on the report of Commission III at the 18th plenary meeting on 19 October 2005. Available from URL: https://www.un.org/ru/documents/decl_conv/declarations/bioethics_and_hr.shtml (accessed 01.10.2024). Russian.
3. Family Code of the Russian Federation dated December 29, 1995 № 223-FZ (as amended on July 31, 2023) (with amendments and additions, entered into force on October 26, 2023) Available from URL: http://pravo.gov.ru/proxy/ips/?docbody&nd=102038925 (accessed 01.10.2024). Russian.
4. Code of the Russian Federation on Administrative Offences dated December 30, 2001 № 195-FZ. Available from URL: https://base.garant.ru/12125267/ (accessed 01.10.2024). Russian.
5. Criminal Code of the Russian Federation dated June 13, 1996 № 63-FZ. Available from URL: http://pravo.gov.ru/proxy/ips/?docbody&nd=102041891 (accessed 01.10.2024). Russian.
6. Law of the Russian Federation “On the fundamentals of protecting the health of citizens in the Russian Federation” dated November 21, 2011 № 323-FZ. Available from URL: http://pravo.gov.ru/proxy/ips/?docbody=&nd=102152259 (accessed 01.10.2024). Russian.
7. Law of the Russian Federation “On psychiatric care and guarantees of the rights of citizens during its provision” dated July 2, 1992 № 3185-1. Available from URL: http://pravo.gov.ru/proxy/ips/?docbody=&nd=102017214 (accessed 01.10.2024). Russian.
8. Law of the Russian Federation “On state regulation in the field of genetic engineering activities” dated July 5, 1996 № 86-FZ. Available from URL: http://pravo.gov.ru/proxy/ips/?docbody=&nd=102042295 (accessed 01.10.2024). Russian.
9. Law of the Russian Federation “On state genomic registration in the Russian Federation”, dated December 3, 2008 № 242-FZ. Available from URL: http://pravo.gov.ru/proxy/ips/?docbody=&nd=102126015 (accessed 01.10.2024). Russian.
10. Law of the Russian Federation of June 23, 2016 № 180-FZ “On biomedical cell products”. Available from URL: http://pravo.gov.ru/proxy/ips/?docbody=&nd=102402596 (accessed 01.10.2024). Russian.
11. Order of the Ministry of Health of the Russian Federation dated April 1, 2016 № 200n “On approval of the rules of good clinical practice.” Available from URL: http://pravo.gov.ru/proxy/ips/?docbody=&nd=102409488&intelsearch=%CD%E0%E4%EB%E5%E6%E0%F9%E0%FF+ %EA%EB%E8%ED%E8%F7%E5%F1%EA%E0%FF+%EF%F0%E0%EA%F2%E8%EA%E0 (accessed 01.10.2024). Russian.
12. Order of the Ministry of Labor and Social Protection of the Russian Federation dated March 21, 2017 № 293n “On approval of the professional standard “Physician (precinct physician).” Available from URL: https://docs.cntd.ru/document/420395834 (accessed 01.10.2024). Russian.
13. GOST R 59812-2021 — National standard of the Russian Federation “Accessibility of urban infrastructure facilities for disabled people.” Available from URL: https://docs.cntd.ru/document/1200181443 (accessed 01.10.2024). Russian.
14. National standard of the Russian Federation GOST R 52379-2005 “Good clinical practice”, approved by order of the Federal Agency for Technical Regulation and Metrology dated September 27, 2005 № 232-st. Available from URL: https://docs.cntd.ru/document/1200041147 (accessed 01.10.2024). Russian.
15. GOST R ISO 14155-2014. “Clinical researches. Good clinical practice.” Available from URL: https://docs.cntd.ru/document/1200110952 (accessed 01.10.2024). Russian.
16. Rules of good clinical practice of the Eurasian Economic Union (approved by the decision of the Council of the Eurasian Economic Commission dated November 3, 2016 № 79). Available from URL: https://docs.eaeunion.org/docs/ru-ru/01411924/cncd_21112016_79 (accessed 01.10.2024). Russian.
17. Code of Professional Ethics for Physicians of the Russian Federation. Accepted by the First National Congress of Doctors of the Russian Federation. Moscow, October 5, 2012. Available from URL: https://docs.cntd.ru/document/561281077 (accessed 01.10.2024). Russian.

Литература

1. «Конституция Российской Федерации» (принята всенародным голосованием 12.12.1993 с изменениями, одобренными в ходе общероссийского голосования 01.07.2020) Режим доступа: [Электронный ресурс] URL: http://pravo.gov.ru/proxy/ips/?docbody=&nd=102027595 (дата обращения 10.01.2024).
2. Всеобщая декларация о биоэтике и правах человека. Принята резолюцией Генеральной конференции ЮНЕСКО по докладу Комиссии III на 18-м пленарном заседании 19 октября 2005 г. Режим доступа: [Электронный ресурс] URL: https://www.un.org/ru/documents/decl_conv/declarations/bioethics_and_hr.shtml (дата обращения 10.01.2024).
3. Семейный кодекс Российской Федерации от 29.12.1995 № 223-ФЗ (ред. от 31.07.2023) (с изм. и доп., вступ. в силу с 26.10.2023) Режим доступа: [Электронный ресурс] URL: http://pravo.gov.ru/proxy/ips/?docbody&nd=102038925 (дата обращения 10.01.2024).
4. Кодекс Российской Федерации об административных правонарушениях от 30.12.2001 № 195-ФЗ. Режим доступа: [Электронный ресурс] URL: https://base.garant.ru/12125267/ (дата обращения 10.01.2024).
5. Уголовный кодекс Российской Федерации от 13.06.1996 № 63-ФЗ. Режим доступа: [Электронный ресурс] URL:

http://pravo.gov.ru/proxy/ips/?docbody&nd=102041891 (дата обращения 10.01.2024).
6. Закон РФ от 21.11.2011 № 323-ФЗ «Об основах охраны здоровья граждан в Российской Федерации». Режим доступа: [Электронный ресурс] URL: http://pravo.gov.ru/proxy/ips/?docbody=&nd=102152259 (дата обращения 10.01.2024).
7. Закон РФ от 02.07.1992 N 3185-1 «О психиатрической помощи и гарантиях прав граждан при ее оказании». Режим доступа: [Электронный ресурс] URL: http://pravo.gov.ru/proxy/ips/?docbody=&nd=102017214 (дата обращения 10.01.2024).
8. Закон РФ от 05.07.1996 № 86-ФЗ «О государственном регулировании в области генно-инженерной деятельности». Режим доступа: [Электронный ресурс] URL: http://pravo.gov.ru/proxy/ips/?docbody=&nd=102042295 (дата обращения 10.01.2024).
9. Закон РФ от 3 декабря 2008 г. № 242-ФЗ «О государственной геномной регистрации в Российской Федерации». Режим доступа: [Электронный ресурс] URL: http://pravo.gov.ru/proxy/ips/?docbody=&nd=102126015 (дата обращения 10.01.2024).
10. Закон РФ от 23 июня 2016 г. № 180-ФЗ «О биомедицинских клеточных продуктах». Режим доступа: [Электронный ресурс] URL: http://pravo.gov.ru/proxy/ips/?docbody=&nd=102402596 (дата обращения 10.01.2024).
11. Приказ Министерства здравоохранения РФ от 1 апреля 2016 г. № 200н «Об утверждении правил надлежащей клинической практики». Режим доступа: [Электронный ресурс] URL: http://pravo.gov.ru/proxy/ips/?docbody=&nd=102409488&intelsearch=%CD%E0%E4%EB%E5%E6%E0%F9%E0%FF+%EA%EB%E8%ED%E8%F7%E5%F1%EA%E0%FF+%EF%F0%E0%EA%F2%E8%EA%E0 (дата обращения 10.01.2024).
12. Приказ Министерства труда и социальной защиты РФ от 21 марта 2017 г. № 293н «Об утверждении профессионального стандарта «Врач-лечебник (врач-терапевт участковый)». Режим доступа: [Электронный ресурс] URL: https://docs.cntd.ru/document/420395834 (дата обращения 10.01.2024).
13. ГОСТ Р 59812-2021 — Национальный стандарт РФ «Доступность для инвалидов объектов городской инфраструктуры». Режим доступа: [Электронный ресурс] URL: https://docs.cntd.ru/document/1200181443 (дата обращения 10.01.2024).
14. Национальный стандарт РФ ГОСТ Р 52379-2005 «Надлежащая клиническая практика», утвержденный приказом Федерального агентства по техническому регулированию и метрологии от 27.09.2005 № 232-ст. Режим доступа: [Электронный ресурс] URL: https://docs.cntd.ru/document/1200041147 (дата обращения 10.01.2024).
15. ГОСТ Р ИСО 14155-2014. «Клинические исследования. Надлежащая клиническая практика». Режим доступа: [Электронный ресурс] URL: https://docs.cntd.ru/document/1200110952 (дата обращения 10.01.2024).
16. Правила надлежащей клинической практики Евразийского экономического союза (утвержденными решением Совета Евразийской экономической комиссии от 3 ноября 2016 г. № 79). Режим доступа: [Электронный ресурс] URL: https://docs.eaeunion.org/docs/ru-ru/01411924/cncd_21112016_79 (дата обращения 10.01.2024).
17. Кодекс профессиональной этики врача Российской Федерации. Принят Первым национальным съездом врачей Российской Федерации. Москва, 5 октября 2012 г. Режим доступа: [Электронный ресурс] URL: https://docs.cntd.ru/document/561281077 (дата обращения 10.01.2024).