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МЕДИЦИНСКАЯ ЭТИКА

НАУЧНЫЙ МЕЖДИСЦИПЛИНАРНЫЙ ЖУРНАЛ
ЯРОСЛАВСКОГО ГОСУДАРСТВЕННОГО МЕДИЦИНСКОГО УНИВЕРСИТЕТА
И РОССИЙСКОГО НАЦИОНАЛЬНОГО ИССЛЕДОВАТЕЛЬСКОГО МЕДИЦИНСКОГО
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МЕДИЦИНСКАЯ ЭТИКА

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ETHICS AND LEGAL REGULATION OF USING LARGE DATABASES IN MEDICINE

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Use of information technologies in medicine resulted in formation of large databases. Analysis of large databases allows to reveal the patterns between the environmental conditions, a way of life and morbidity, that promote a progressive study of pathogenesis, clinical course, disease prognosis, and accelerate clinical trials of novel treatment options. Large databases are most in demand in bioinformatics and biomedicine. The issues of using large databases are associated with a number of ethical issues such as confidentiality, informed consent, and privacy. Ethical issues of using personal medical data were reflected in international documents. The use of large databases is associated with a dilemma of legislative protection of patients' rights, on the one hand, and a decrease in analytical capabilities of using the data, on the other hand. Several methods of medical data safety are suggested to prevent identification of patients. Depersonilized data belong to one way of solving the issues. The options of studying secondary medical data are being discussed.

Keywords: large database, biomedical ethics, informed consent legal regulation

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ЭТИКА И ПРАВОВОЕ РЕГУЛИРОВАНИЕ ИСПОЛЬЗОВАНИЯ БОЛЬШИХ БАЗ ДАННЫХ В МЕДИЦИНЕ

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Внедрение информационных технологий в медицине способствовало формированию больших баз данных. Анализ больших баз данных позволяет выявить закономерности между условиями окружающей среды, образом жизни и заболеваемостью, которые способствуют прогрессу изучения патогенеза, клинического течения, прогноза заболеваний, а также ускорить клинические исследования новых методов лечения. Наиболее востребованы большие базы в биоинформатике и биомедицине. Проблемы использования больших баз связаны с рядом этических проблем: конфиденциальностью, информированным согласием, неприкосновенностью частной жизни. Этические вопросы использования персональных медицинских данных нашли отражение в международных документах. Использование больших баз данных сопряжено с дилеммой, обусловленной, с одной стороны, законодательной защитой прав пациентов, а с другой — снижением аналитических возможностей использования информации. Предлагается несколько методов безопасности медицинских данных для предотвращения идентификации пациентов. Одним из способов решения этой проблемы является деперсонифицированность данных. Обсуждаются варианты возможности исследования вторичных медицинских данных.

Ключевые слова: большие базы данных, биомедицинская этика, информированное согласие, правовое регулирование

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SINGLE INFORMATION DATABASE IN RUSSIAN HEALTHCARE

In healthcare of the Russian Federation, transition to digital medicine is being implemented at an accelerated pace. The strategy of healthcare digital transformation includes formation of a single digital circuit, medical platform solutions taken at the federal level, personal medical assistants and artificial intelligence. Implementation of new projects is aimed at a single approach to provision of medical aid, implementation of the control system, statistical accounting and analysis, use of electronic documents to manage the healthcare system. The planned wide application of information technologies in medicine should correspond to ethical standards and rely on the legislative base.

Resolution of the Government of the Russian Federation as of February 09, 2022 No. 140 'About a single state information system in healthcare (SSISH)' was issued to improve information technologies [1]. The SSISH should provide connection between all regional medical organizations. Its functions include processing and storage of medical documentation and health-related data, providing analytical information based on anonymous personal data to be subsequently used in statistics and research, and to develop and apply solutions driven by artificial intelligence. The SSISH should bring together information about drug provision to citizens including those who have a right for preferential provision of medicines and medical products, include federal bases of medical documents about death and birth, structured electronic medical cards, centralized systems named 'Laboratory research' and 'Central archive of medical images'.

The single information database in healthcare will improve interaction between medical institutions, increase accessibility and effectiveness while providing medical aid, including the one rendered using artificial intelligence and telemedical consultations.

LARGE DATABASES IN MEDICINE

Medical data collection and archiving in medicine have a long history. Accumulation of big data in healthcare using information technologies greatly expands the possibilities of their use and can become an effective tool both for development of practical medicine, and for scientific purposes to examine prevalence and pathogenesis of diseases, revealing risk factors and developing new effective methods of treatment. Use of medical cards, including electronic ones (EMC), and other medical documentation in Big Data is associated with a number of difficulties such as unproperly filled EMC, unnecessary duplication of data, lack of data completeness and single system of EMC management, and lack of structured records. Organizational problems are related to outdated technologies in separate medical organizations and lack of united regulatory and reference information.

Implementation of the healthcare digital transformation project with SSISH formation is aimed at elimination of the abovementioned problems. This allows to use the database in scientific research. Information technology capabilities allow to use the EMC right now. To retrieve the data from the EMC and perform machine processing, special preparation is required, including retrieval of data using artificial intelligence and other technologies that allow to retrieve the data from unstructured records, cleaning, transformation, filtration, separation, translation, uniting, sorting and checking the data [2].

In modern medicine, Big Data are most in demand in bioinformatics and biomedicine. Genome sequencing projects include thousands of people, animals, insects and microorganisms. Use of large databases expands diagnostic capabilities of interpretation of results obtained during massive parallel sequencing. The research results are applied to determine the risk of diseases, diagnostics, including prenatal testing, prognosis of the course of diseases, and producing qualitatively novel drugs. Technologies that use large databases are used to study the microbiome. The databases contain data as billions of short readings that can be extended to create compositional and functional profiles of hundreds and thousands of microbes within this microbiome [3].

Use of big data and block chains in pharmacology allows to significantly expand a number of research centers and reduce the duration of clinical trials of medicines. Use of Big Data in systemic biology and medicine allows to detect markers that predict various diseases. To search for the biomarkers, models of multiple effects are used to detect their association with an immunome and epigenetics (targets for microRNA and DNA methylation and telomere length). The environmental effect on the body depending on the genetic status is assessed [4]. The capabilities of prediction of catastrophic events, including epidemics, are expanded using big data and artificial intelligence [5].

Big data are analyzed and used in every sphere of life. It is expected that in the future a third part of information data available in the world can be attributed to healthcare. Apart from EMC, large databases use medical registries of various diseases (HIV-infection, TB, oncological diseases, etc.), bases of cohort and clinical trials, biobanks and panomics. The existing databases include thousands to millions of people already now. For instance, the Danish DOC * X cohort includes social and economic data and health-related information related to over 6 million adults and 1.2 million children, genomic data of the British biobank involve nearly half a million of British citizens, database 'Multiple-Parameter Intellectual Monitoring in Intensive Therapy II' (MIMIC–II) involves about 30,000 patients from the department of intensive therapy.

ETHICAL ISSUES OF USING LARGE DATABASES

Medical Big Data include demographic data, results of laboratory and instrumental studies, and information about the conducted treatment. Use of patient-related data poses ethical questions to researchers. Biomedical data constitute secure medical information protected by the legislation. Right for confidentiality means that personal data submitted by patients will not be displayed without their permission, except for the cases set ethically and legally. Healthcare information technologies include protection of data integrity and confidentiality. In accordance with regulating documents, data depersonalization is one of basic requirements by SSISH [6]. This significantly limits the capability to interpret the obtained results including assessment of the environmental role, hygienic characteristics of living conditions, manufacturing factors of risk, and features of the healthcare system in the region of residency. Epidemiological, ecological, geographical, climatic, demographic data, analysis of social networks, statistical data of medical institutions, economical and sociological values are currently used to examine the effect of various factors on the change in biomarkers. These data are not covered by the Medical Secrecy Law. However, analysis of large databases enables to detect individuals with peculiar characteristics by indirect values. For instance, provision of medicines reveals patients with HIV, TB, orphan diseases, etc. Digital footprint technology violates privacy. Social media monitoring allows to

predict the risk of suicide and wrongful acts. Data loss from the registries of patients with disability, genetic disturbances, mental diseases, alcohol abuse, drug addiction may lead to discrimination during employment, insurance, crediting and other negative social consequences. Data bases are of interest both for commercial structures, and state authorities.

Analysis of ethical problems occurring while using large bases performed by Ienca M. et al. has shown that personal privacy and confidentiality belong to the dominant problem (n = 146), followed by the issues of informed consent (n = 49), honesty and justice (n = 34), trust (n = 23), right of ownership, etc. (fig.) [7].

Use of large databases highlighted a number of new ethical issues. Analysis of interaction between large database values and ethnic features, geographical location, environmental pollution makes it necessary to protect considering the group identity. Data about predisposition of a large group of people united by certain attributes to mental, genetic diseases, gender identity, drug addiction, and juvenile delinquency can lead to problems of individuals in various spheres of life. The Council of Europe offered to accept the right 'not to be subjected to profiling' as a new right to prevent discrimination against certain persons or groups of persons [8].

Use of big data allows to reveal patterns between environmental conditions, a way of life and morbidity. Ethical risks associated with the use of these data are not just about developing recommendations but also about urging to change the way of life at the state level leading to restriction of an individual right to privacy. Interpretation of data obtained during analysis of large bases constitutes another ethical issue. High level of evidence is observed due to inclusion of a large number of patients based on large databases. However, the results can depend on experience and good faith of institutions and persons who analyze and interpret the databases. The results obtained during analysis of large databases do not have demonstrability and require an additional inspection and addition of data provided by other trials [9].

LEGAL REGULATION OF USING LARGE DATABASES

Issues of biomedical ethics while using large databases are considered in documents of various countries.

- Big data: using capabilities and preserving values (Administration of U. S. President, 2014) [10].
- Collection, binding and using data in biomedical research and healthcare: ethical issues, Nuffield Council on Bioethics (Great Britain, 2015) [11].
- Big data and sovereignty of medical data as building information freedom (German Ethics Council, 2017) [12].
- Code of Ethics of IMIA for specialists in medical informatics and Code of professional and ethical behavior of AMIA [13, 14].

Ethical issues of using personal medical data are documented in international instruments. In 2016, the World Medical Association published a declaration about ethical considerations in relation to healthcare data bases and biobanks [15]. In 2016, (EU) Regulation 2016/679 of the European Parliament and Council on protection of individuals while treating personal data and on free movement of these data was accepted in Europe [16]. In 2017, the Report from the International Bioethics Committee of UNESCO on Big Data and Health was accepted (2017) [8].

ALTERNATE SOLUTIONS OF ETHICAL ISSUES OF USING LARGE DATABASES

Solving confidentiality-related ethical issues provides several algorithms of safety of medical data aimed at the information system of safe storage, creation of programs that exclude any connection between real and pseudoidentification data. Data encryption (key, algorithm) that could identify a patient and the access code in the form of a password are used to improve safety. A safety measure includes a capability of utilizing 'empty pseudoidentifications' that improve safety by neutralizing the possibility to compare information data with a real personality [17].

The method of pseudonymization when identification data are transformed and then replaced by a specifier that can't be associated with identification data without reference to a certain password is suggested to protect data. Confidentiality means excluding storage of personal information with pseudonymized data making it necessary to form two bases: one having personal data and the other one with pseudonymized information.

A wider model is based on protection of access to database by storage encryption with access keys for service personnel. However, even such models of 'access control' can be bypassed using information technologies or people operating inside the system [18].

Every country has a regulatory agency which takes into account patients' interest and regulates the market of medical services. It is about the Roszdravnadzor in Russia and Food and Drug Administration in the U. S. In Russia, confidentiality protection significantly limits access to medical data. It is the patient who owns biomedical data. Data access and treatment are possible only in case of permission taken from the person who signed the informed consent form. The company that grants the permission and

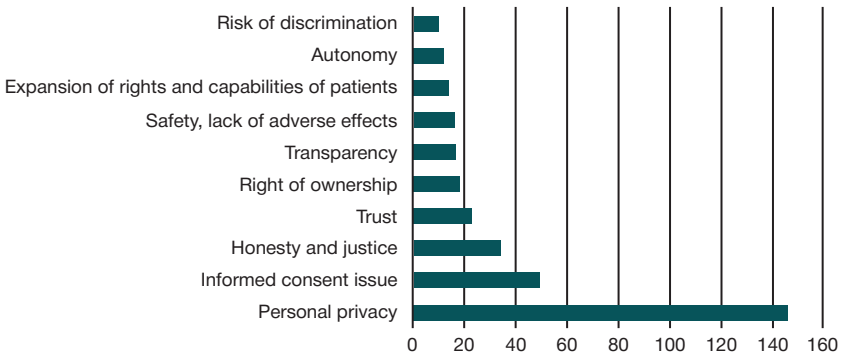

Fig. Rate of ethical issues associated with big data research in medicine (Ienca M, et al. 2018)

purposes of data collection and treatment are mentioned in the form.

The use of large databases is currently associated with a dilemma posed by the legislative protection of patients' rights, on the one hand, and decrease in analytical capabilities of data use, on the other hand [19]. Depersonilization of data and possibility of their use without a patient's consent could be solution to this problem. Today, the legislation in Russia allows using the depersonalized data only within a medical institution that obtained permission via the mentioned goals in accordance with the mentioned purposes. In perspective, it requires a change in the legislation to utilize depersonalized data without a patient's consent meaning transfer of data ownership to the state. It is necessary to form an authority that could be responsible for data storage and regulate its usage.

The study of secondary medical data is usually carried out when a patient's consent is obtained or when data are completely anonymous. Today, an informed consent is commonly granted once (at hospitalization, inclusion into a clinical trial, etc.). It limits the use of databases for retrospective assessment or for other research purposes. The practice of obtaining the Dynamic Consent in some countries means temporary renewal of consent to use data when patients can provide a repeated consent to the use of data which can also be different from the first one. It could facilitate cooperation with a patient and expand their capability to control the use of data. The practice of granting the Wide Consent means using data within more than one clinical trial if the projects are related to a certain area or direction of the trials [8].

CONCLUSION

Big data analysis enables to reveal the patterns of influence of various factors on biosystems, expands the capabilities of clinical trials, medical education, clinical practice, improves identification and prevention of diseases, assessment of treatment effectiveness and prediction. Healthcare big data analysis opens up a huge potential for scientific research, on the one hand, and increases the risk of accessibility to personal data of the patients, on the other hand [20].

Ethics of using large databases should be based on solving the following tasks:

- strengthening control over data storage and usage;
- respecting the privacy of individuals and groups of individuals having the same profiles;
- informed consent to data transfer and proper practice in relation to the ways of their obtaining;
- responsibility of medical workers, researchers, managers and computer specialists for their professional activity while dealing with big bases.

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LEVELS OF EVIDENCE AND STUDY DESIGNS

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In this article, various designs of clinical trials used to obtain new scientific knowledge in the field of clinical medicine are considered from the position of their evidential value in studying the cause-and-effect relationship between the influencing factor and result of its potential effect on human health. Basic differences between observational and experimental trials, their limitations due to peculiarities of design of clinical trials are being discussed. A conclusion is made that validity of results of clinical trials should be assessed taking into account the limitations that are typical of various designs. Accuracy of clinical trials depends on many factors that can distort the obtained results as compared with true values. It is noted that observational trials are subject to systematic and accidental errors to a greater extent than experimental ones. It occurs because design characteristics do not allow observational trials to control the mistakes associated with possible incompatibility of comparison groups. They can detect a statistical relation between the phenomena, but only randomized clinical trials can prove that there is a causal relationship. Accuracy of a randomized clinical trial can be increased using systematic reviews and meta-analysis.

Keywords: designs of clinical trials, observational controlled trials, experimental clinical trials, systematic review, meta-analysis, systematic errors, substantiation of conclusions, evidence reliability levels, recommendation strength levels

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ДОКАЗАТЕЛЬНОСТЬ КЛИНИЧЕСКИХ ИССЛЕДОВАНИЙ РАЗЛИЧНЫХ ДИЗАЙНОВ

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В данной статье различные дизайны клинических исследований, которые используются для получения новых научных знаний в области клинической медицины, рассматриваются с позиций их доказательной ценности в изучении причинно-следственных взаимоотношений между воздействующим фактором и результатом его потенциального влияния на здоровье людей. Обсуждаются основные различия между наблюдательными и экспериментальными исследованиями, а также их ограничения, обусловленные особенностями дизайнов клинических исследований. В заключение делается вывод о том, что к оценке достоверности результатов клинических исследований надо подходить с пониманием тех ограничений, которые характерны для различных дизайнов. Точность клинических исследований зависит от влияния многих факторов, которые способны приводить к искажению получаемых результатов по сравнению с их истинными значениями. При этом отмечается, что наблюдательные исследования подвержены систематическим и случайным ошибкам в большей степени, чем экспериментальные. Это объясняется тем, что в силу особенностей дизайна наблюдательные исследования не могут контролировать ошибки, связанные с возможной несопоставимостью групп сравнения. Они способны выявлять наличие статистической связи между явлениями, но доказать, что связь носит причинно-следственный характер, могут только рандомизированные клинические исследования. Точность рандомизированного клинического исследования может быть повышена с помощью систематических обзоров с метаанализом.

Ключевые слова: дизайны клинических исследований, наблюдательные контролируемые исследования, экспериментальные клинические исследования, систематический обзор, метаанализ, систематические ошибки, доказательность выводов, уровни достоверности доказательств, уровни убедительности рекомендаций

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Getting new scientific knowledge in the field of modern clinical medicine is mainly based on the results of clinical epidemiological trials. They enable to detect the factors leading to occurrence and progression of diseases, estimate the quantitative input of these factors into development and subsequent course of diseases, stratify a population by the extent of risk and determine prognosis, monitor the level of risk factors and estimate effectiveness of preventive programs, plan clinical trials, formulate and check hypotheses.

The role of dyslipidemia, arterial hypertension, smoking and diabetes mellitus in development of atherosclerosis and associated diseases was mainly revealed owing to epidemiological trials. Clinical trials (CT) were conducted and treatment and prevention recommendations of these diseases were developed both at the population and individual levels [1].

In clinical epidemiology, several types of CT are used. They have different structures and are aimed at searching answers regarding some clinical issues about assessment of prevalence of pathological conditions, searching and studying the reasons or factors of risk of diseases, assessment of frequency, relative risk and prognosis of morbidity. The principal clinical issues

include assessment of effectiveness of preventive, diagnostic and therapeutic medical interventions.

Every task can be solved using a CT with a certain logical structure that includes methods of enrolling people into a trial, formation of comparison groups, collection of data, and methods of its analysis and interpretation. Design is a trial form created to search for answers to the set clinical questions. The design reveals a degree of accuracy for the result obtained during the trial, which shows real connections between the events.

In this article, attention is given to the factors that limit the degree of trial reliability associated with survey design; the structure and degree of reliability of various designs in comparative terms are considered. Recommendations regarding determination of evidence reliability levels and evidence strength levels are provided.

ACCURACY OF RESEARCH

Reliability of the trial is determined by its accuracy, which consists of the extent with which the results can be applied to other groups (external validity or generalizability), extent to which the trial can exclude the alternative explanation of the obtained results (internal validity) and extent of exact assessment of measured results (confidence) [2].

External sample validity is determined by the extent of representativity as related to its population [3]. Scientific clinical trials involve not the entire population suffering from the studied pathology or to whom the assumed risk factor is applied, but a part of this population (sample). If characteristics of these participants completely correspond to those of the population, i. e., the populations are representative, the obtained results can be applied to all people from this population. However, the sample can be representative only if it was formed using the random selection method. The random selection method deals with selection of all patients with this pathology and subsequent accidental or equally probable inclusion of representatives of all types of patients from the general population into the sample.

In medical trials, this is almost impossible. Thus, patients from clinical trials can differ from all the patients with the studied disease by age, gender and nationality, social status, material wealth, attitude to health, location, condition severity and many other characteristics. It makes the sample not accidental and not quite representative. In this case, the external sample validity is insufficient.

Conclusions associated with non-random samples can be applied to the general population with a certain proportion of errors (bias). This error occurs during sample formation and is called a systematic sample error.

In statistics, **a systematic error** means unintentional, but regular, non-accidental and unidirectional deviation of the calculated indicators from their actual values [4].

The less is the sample representative, the less exact is the trial, the more likely it is that other factors (errors) that distort conclusions influenced the trial results. The sample representativeness can be increased with numbers, thus, our trust in trials with a higher number of participants is stronger.

Internal validity is determined by how well the trial design can exclude alternative explanations of these conclusions. Differences in the results of the compared groups are not a mere consequence of the studied factor. There are other explanations, too. We can't exclude an effect on the result of other functions, which the researcher didn't plan to trial, failed to take into account or which he wasn't aware of, but which can also influence the outcome.

In case of irregular distribution of these factors among groups of comparison and control, effect of these factors will displace true results of the intervention and lead to inaccurate and erroneous conclusions. The factors cause unilateral bias (distortion) of trial results and are called systematic selection errors. The selection errors include all the factors that lead to incomparability of the studied group and control group.

The results of clinical trials can be influenced by other systematic errors such as errors obtained while collecting information, memory errors, withdrawal-related errors, errors that occur while assessing and analyzing the results, and some others [5, 6]. All systematic errors can make the differences visible, though they do not exist in reality, or, on the contrary, the real existing differences can be hidden. A systematic error can arise in any observations and at any stage of the trial. The sample size does not influence the systematic error value.

To be sure that the observed result is a consequence of the studied factor but not systematic errors, their significance should be excluded or reduced. This is achieved during sampling through increasing its representativeness or at the stage when comparison groups are formed during randomization. They can also be partially taken into account while analyzing the trial results. The principal method that minimizes the effect of the majority of systematic errors is represented by randomization, i. e., accidental distribution of patients among comparison groups. Meanwhile, systematic errors are also regularly distributed among comparison groups and fail producing the bias effect if the groups are large enough.

RELIABILITY OF RESEARCH

An accidental error is another explanation of differences in the results among the compared groups. **An accidental error** is a deviation of a single observation (or measurement) from its true value that occurs while processing accounting documents, during measurement or registration of data due to an accidental combination of circumstances. There is an equal probability that an accidental error can result in overestimation or underestimation of research results. Any observations are exposed to accidents. Complete exclusion of accidental errors is not possible though they can be minimized using more exact methods of trial parameter estimation, for instance, standardized ones, or by increasing a number of patients in a trial.

An accidental error can be estimated and accounted at the stage of statistical analysis of results, which allows to answer a question about the probability of obtaining the results in an accidental way. In medical research, the accessible level of probability of getting an accidental result arises when p is less than 0.05 [7].

The marked accidental error is commonly observed in small samples with highly non-homogenous characteristics (both inhabitants of cities and villages, men and women, those with and without bad habits of a wide range of ages are included). The higher the sample heterogeneity, the greater the probability of an accidental error and the more people should be included into comparison groups to increase the reliability of conclusions. Even a marked accidental error does not provide for a bias (does not distort the research result), but may prevent revealing statistical reliability of the obtained results.

The level of systematic errors is controlled by strict fulfillment of design requirements. Owing to design characteristics, clinical trials can control the effect of systematic errors to a different extent and can have certain limitations regarding the degree of reliability. It should be noted that some factors such as the use

of improper statistical methods of analysis, lack of adjustment for systematic and accidental errors, negligent data handling can distort the trial results irrespective of the selected design.

Clinical trials with various designs are used in scientific medicine. Three basic designs can be found among them. Their task is to find and examine the causal relationships. They include case-control trials, cohort trials and randomized clinical trials [8, 9].

DESIGN AND EVIDENTIAL VALUE OF CASE-CONTROL TRIALS

These are observational trials when researchers do not only interfere in the natural course of disease occurrence and distribution. They only observe how the situation that doesn't depend on them is developed, collect data on the examined issue and make conclusions [10].

Case-control trials are used to reveal unknown risk factors of known diseases. To detect the relation between the clinical outcome and preceding effect of the assumed factor, two groups of people are included into the trial. The main group includes those with a disease or condition that seems interesting to the researchers. The group is called 'cases'. The control group involves people without such a disease or condition. A history of all trial participants includes presence or absence of certain factors that could be the reason for development of the studied disease. The both groups are then compared by the rate of potential risk factors for this outcome, and the statistical significance of these differences is determined.

The feature of the case-control trial means that this design doesn't mean randomization while making comparison groups, leading to incomplete comparison of the main and control groups due to systematic errors.

A number of 'cases' is selected among patients with the studied disease or condition and to whom the researcher would like to disseminate the conclusions he is determined to obtain. The group of 'cases' should always be representative of the studied population. Insufficient representativity of the group of 'cases' (sampling error) can result in unproper generalization of the trial results.

The researcher selects a group of 'controls' based on characteristics of the 'case' group but not in the result of randomization, which is a source of systematic selection failure. When selecting the control persons, the main condition consists in their maximum comparison with a group of cases based on all the basic characteristics, except for the studied disease. To obtain a more reliable result, a group of 'controls' should be comparable with a group of 'cases' to the greatest extent [11]. For this, 'controls' should be selected from the same population as the 'cases', preferably during the same period of time. For instance, both the 'cases', and the 'controls' should be selected from among the people admitted at the same hospital, receiving treatment at the same outpatient clinic, living in the same district or working at the same enterprise.

In case of insufficient comparison, cases and controls can differ by the condition severity, concomitant pathology, social status, bad habits, and use of medicines influencing one's health, etc. [12].

To reduce the selection error, a paired design is used. It ensures an individual selection of 'cases' for every group participant that corresponds by a set of characteristics to a control group participant [13]. As a result, researchers obtain almost similar groups of comparison with the only difference: presence or absence of the studied disease.

One of the systematic selection errors, when a true result is displayed in a wrong way, can be due to an effect of an unknown or unaccounted factor. The factor can produce a simultaneous influence both on the outcome, and on the studied factor of the disease. The factor is called 'a confounding factor' or 'a confusing variable' (confounder) [14].

A trial that examined a link between a birth order (1st, 2nd, 3rd child, etc.) and presence of Down's disease can serve as an example. In this trial, maternal age will be a confusing variable as it influences both the outcome (a higher maternal age is directly associated with a possible development of Down's syndrome in a child) and a birth order when every next child, except for twins, is born when the mother is older than she was when she gave birth to the 1st child.

The presence of confusing factors can be clear or not. Thus, the conclusions obtained based on observational trials can fail to display a real effect of using the examined intervention.

Retrospective trials have typical systematic **errors at the stage of data collection and memory errors**. During case-control trials, a search for causal relationships always moves from a consequence to the assumed reason, i. e., retrospectively. At the initial stage of a retrospective trial, a researcher has already been informed of an interesting outcome and collects data about the events (possible risk factors) that took place in the past. Medical records or outpatient cards stored at healthcare organizations (i. e., secondary information), recollections of patients, interviews with their relatives or questioning results constitute a source of information. This is associated with occurrence of information systematic errors and memory errors. Data registered in medical documentation were collected for other purposes and tasks, the researcher failed to participate in their collection and frequently doesn't know who and when collected the data.

Archive information may not correspond to the purpose of the conducted trial to the full extent, it may not be collected properly and some data can be lacking. Data collected from people can insufficiently reflect the events of the past. Selective memory of a patient and healthy person can make a difference.

For instance, a sick person can recollect the events potentially related to occurrence of this disease better than a healthy one, and fail to recollect certain facts that can seem interesting to a researcher. Memory failures are particularly true if they relate to data about the effect of the studied risk factor, which is a principal shortcoming of all retrospective trials [5].

Data registered in medical documents were collected for other purposes and tasks, whereas the researcher didn't participate in their collection and frequently does not know who and when gathered the data.

Along with sampling errors, selection errors and data collection errors, case control trials are not protected from accidental errors, providing many alternative explanations to the obtained results. Substantiation of this type of trials is not very high.

Statement of hypotheses about disease risk factors and conditions form the result of the trial. The hypotheses should be confirmed during more exact cohort trials.

Though the case-control trial doesn't prove there is a causal relationship, such trials are the only suitable ones to study the risk factors of rare diseases [7].

DESIGN AND EVIDENTIARY VALUE OF COHORT TRIALS

Cohort trials are also observational. The data are collected by observing events without a researcher's intervention [8].

The purpose of the trial is to search and detect unknown consequences of effects by assumed risk factors on human health and examination of interrelations. For the study purposes,

a group of people (cohort) that should be a representative sample of the population is selected from a general set (population). A cohort is a group of people with common characteristics or experience during a certain period of time when new disease cases are expected to occur. People living in the same city, exposure to hazardous substances, undergoing a certain medical procedure, belonging to representatives of the same profession or social group, being born at a certain period of time, etc. belong to a unifying feature.

The examined cohort is represented by people influenced by the examined risk factor, whereas the control cohort includes people not influenced by the examined factor [15]. The control group is selected from the same population the cohort is composed of or another cohort that was affected little or not affected at all, with all the other characteristics being most similar to those of the studied group. These cohorts are observed for some period of time to understand, which outcomes can lead to this risk factor. An obligatory condition of inclusion of these people into the examined and control cohorts is represented by a lack of the studied disease at study enrollment.

Then the both groups are compared by the rate of disease development, the value of relative risk that confirms the relation between a risk factor and outcome probability is determined and the statistical significance of differences is estimated.

Cohort trials are called prospective if the search for the causal relationship moves from the reason to the assumed effect. In other words, the cohort is being observed from initiation of the trial when the disease is still lacking; the observation is being continued for a period enough for the assumed outcome to develop. Meanwhile, the researcher can't know the outcomes beforehand excluding subjectivity while selecting those analyzed. In this case, the source of data is represented by data assumed to obtain during a trial and independently registered by the investigators, that's why they are more reliable and correspond to the study purposes to a greater extent.

Cohort trials can be retrospective when at the beginning a researcher has information at his disposal and collects data about the events that took place in the past. However, the groups are formed depending on the presence or absence of risk factors. Like in other retrospective trials, data are collected using archival documents (case history, questionnaires, results of participants' survey, etc.). The researcher analyzes the past data by tracing morbidity and mortality for all members of the studied groups until now [15].

Cohort trials are not exempt from systematic and accidental errors. **Errors related to cohort representativeness** can occur if its composition does not completely correspond to the population it was selected from [16]. The situation is possible when the cohort includes visitors of a certain medical center where the patients can enter not accidentally but because they live nearby or where they can be referred because of a severe condition or because they can pay for the medical services, whereas the general population includes not only patients of medical centers but also those from municipal hospitals and outpatient clinics. The differences can relate to the age, gender, social and economic status, living conditions, health, etc. It is sometimes difficult to generalize the results even of large clinical trials.

For instance, it is difficult to determine the rate of representativeness of a rich American city Framingham (Framingham trial of IHD risk factors) at least for the USA, or that of the trial on British doctors at least for representatives of other professions in Great Britain (trial of the association between cigarettes and lung cancer).

Correct cohort assessment influences the possibility to transfer the data obtained during the trial to the initial population and population with similar characteristics. The larger is its size, the more exact are the obtained data, the more they correspond to the general population [17].

Data and memory errors while conducting cohort trials with retrospective collection of data show that it is difficult to reconstruct the events of the past without distortions. Some documents recording the effect (for instance, a harmful factor in the past) can be lost, whereas recollections of relatives are not exact. Data collection and memory errors result in masking the influencing effect and distorted conclusions.

Another error observed during prospective cohort trials is represented by the **error of withdrawal from the study**. Depending on the examined disease, prospective cohort trials can last for a long time — for years or even for decades. In such duration of observations, some patients can withdraw from the study due to their shift to another place of residence, refusal to participate, death, loss of contacts, etc. A decreased number of cohorts is associated with reduced statistical power and, as a consequence, less reliability of the study. It is believed that when over 10% of the cohort is lost, the study results are doubtful, whereas dropout of over 20% of participants displays its uncertainty [9, 18].

Cohort trials can be associated with **selection errors** that include all the factors except for the examined ones, which, in case of irregular distribution between the studied and control cohorts, can result in the lack of their compatibility and influence the study results.

Examples can include differences in treatment, number of visits to doctors or any other values. Inclusion of patients into trials at different times can result in significant differences among the compared groups. For instance, during mixed retrospective and prospective trials no difference in terms and exact diagnosis, past approaches to therapy (say, 15 years ago) and today can be taken into account. In this case, changed outcomes can rather be explained by a difference in assessment of disease severity than by treatment effect.

Undocumented or unknown confounding factors are found among the factors that can be a source of a systematic error. The confounding factors produce such an effect that the effect of the studied factor can be overestimated or underestimated. To exclude the effect of known confounders, the both groups should be comparable to the greatest extent by the largest number of parameters, except for the examined ones [19]. While analyzing data, there are methods enabling to consider the effect of all factors we are aware of. But even after all amendments the confounding factors not known to us can be left unaccounted. The balance of unknown confounders is achieved through randomization. Randomization in cohort trials is impossible, as the observational approach to studying the relations between the events excludes accidental distribution of people into the compared groups.

Impossible control over unknown confounders is a serious disadvantage, that makes observational trials different from a randomized experiment. Unfortunately, it is impossible to get rid of this shortcoming of observational trials. That's why we get an uncomplete level of evidence of observational trials, and cohort trials, in particular [14].

Though prospective cohort trials do not exclude all the possible mistakes, they are the most evidence-based among observational trials and reflect a causal relationship in a more precise way. Cohort design is considered the best when it is necessary to examine the effect of potentially harmful risk factors on disease occurrence, i. e., when human experiments are not possible.

DESIGN AND EVIDENTIAL VALUE OF RANDOMIZED CLINICAL TRIALS

A randomized clinical trial (RCT) is an experimental study where a researcher simulates a clinical situation which suits the best to examine the causal relations between the studied phenomena. As a rule, experimental trials are conducted to check the cause-and-effect hypotheses while examining effectiveness of various methods of treatment and prevention, both drug-induced, and not.

In experimental trials, it is ethically acceptable to examine only the effects of factors, which, as assumed, deliver benefit to a patient. Thus, artificial intervention into the natural history of events occurs at the expense or with the elimination of suspected factors that cause diseases or while administering medicinal agents, using methods or performing activities able to produce a favorable effect on the studied disease [20–22].

Design of a RCT is much like design of cohort trials. A group of people which is a representative sample is selected from the general set (population) based on strict criteria of inclusion and exclusion. Then the included patients are accidentally (irrespective of a researcher's will) distributed into the study group (obtain the studied intervention) and control group (obtain placebo or known intervention with known effectiveness). During the trial, the participants are under a planned observation with registration of their subjective and objective condition. At the end of the trial, the differences in the results of the both groups are assessed along with their statistical significance.

Experimental trials can be prospective, retrospective and mixed (historical control study). During a prospective trial, the researcher should collect and register data about a patient; during a prospective trial, data are collected using archival medical documentation or interviews of patients, decreasing the reliability.

Design of the RCT differs from other types of trials by the possible procedure of randomization. It is the randomization that allows to neutralize the significance of the majority of systematic errors occurring during a CT. They involve **systematic errors creating a disbalance between the comparison groups including confounding.** Thus, there is a low probability that the obtained results are not due to the studied intervention, but have an alternative explanation. However, it is true only when the researcher fails to violate the basic randomization principle. According to it, every sampling member should have equal chances to be included both in the studied group, and in the control group [23].

The reason for incorrect randomization is inclusion of patients into the group of comparison by indications, order of selection, days of the week, case history numbers, insurance policy or date of birth. These grounds introduce a systematic error into the process of formation of comparison groups. It is better to use a table of accidental figures, methods of envelopes or centralized computer distribution of treatment options.

When the principle of equal changes is violated, no regular distribution of the effect of systematic errors occurs and the evidence level of this trial goes down reaching the level of cohort observation [20].

Randomized historic control trials are less exact as compared with prospective ones due to **errors that occur during collection of data and memory errors**, and because of possible differences in diagnostic criteria and accuracy of the examination of patients from the control group. **A systematic error associated with withdrawal** of patients from the long-term study requires correction at the stage of result assessment.

The randomized trials do not completely exclude **sampling errors** that reduce the possibility to apply the obtained results to a wider population of patients. For instance, the majority of RCT are conducted with relatively young patients without concomitant diseases, whereas the medicinal agents studied under these conditions are consumed by elder patients suffering from many diseases. Randomized trials performed on selective groups have low representativity. The use of selective groups is justified while studying a novel medicinal product to confirm its pharmacological activity and determining its safe doses during the first stages of CT.

It is desirable to detect and eliminate some **systematic errors associated with positive expectations** of patients related to their participation in a CT (placebo effect) at the stage of selection. It is necessary because different expectations of patients in the compared groups can influence the study results to the greatest extent. Psychological patterns and expectations arise not only among patients, but also among medical personnel who conducts the study. It is due to a prejudiced attitude of an investigator while selecting patients and subjectivity when assessing the borderline results of the study. To exclude these psychological phenomena, it is necessary to limit awareness of researchers concerning the provided medicinal agents in the comparison groups (blind, double-blind trials). It is shown that a lack of double blinding can increase effectiveness of medicinal agents by 15–20% in average [21].

The use of a blind method regarding to patients, doctors and researchers estimating the clinical outcomes and statisticians enables significantly reduce the probability of a systematic error of that type.

In spite of the randomization, the compared groups can be heterogenous due to insufficient sampling size and associated increased effect of an **accidental error**. The probability of an accidental error is increased in case of high heterogeneity (nonuniformity) of the population that constitutes the sample.

Thus, small RCT or RCT held in one center only, have insufficient representativity (non-homogenous sample), reduced internal validity (disbalance of compared groups) and insufficient reliability (increased probability of an accidental error). As the accidental error and sample heterogeneity are decreased with size, trust in large multi-centered RCT is always higher. To ensure better reliability, it is necessary to perform multiple checks of RCT results to prove the causal relationship. It is desirable that the study should be repeated by various researchers on many differentiated samples, at different time and under various conditions. It is impossible to completely exclude the effect of an accidental error, that's why there is always 5-percent probability that the result obtained during the study is due to accidental occurrence of circumstances [24].

In spite of possible problems, properly planned and conducted RCT enable to obtain highly significant conclusions and are a golden standard of evidence-based CT.

STRUCTURE AND EVIDENTIAL VALUE OF SYSTEMATIC REVIEW AND META-ANALYSIS

As even RCT are not very exact, methods of evidence-based medicine such as systematic reviews including or excluding meta-analysis have been developed.

A systematic review (SR) is an analytical study of analytical observational and experimental trials presented in literature and serves as a tool of secondary analysis of scientific publications.

The study begins with the formulation of a clinical issue that requires an answer. It is about effectiveness of treatment, prevention or diagnostic methods. The best works that are used to investigate the same problem and that have a similar structure possess the most powerful design and are conducted in the most scrupulous manner. The trials are selected based on distinct inclusion and exclusion criteria, which should be substantiated and determined beforehand. Then the results of all trials that passed the selection are generalized. An answer to the clinical question is provided based on these generalized results. It can be expressed as a confirmed causal relationship, its denial or when qualitatively conducted primary trials are not enough to give a definite answer to the question [25].

The source of data for SR is constituted by all discovered published analytical observational and experimental trials about the examined clinical issue. The data are searched through electronic information data bases, which include only materials that correspond to certain criteria of methodological quality. These are Medline, Embase, Cochrane Library, and eLibrary.ru.

However, not all trials can be included into SR, as SR generalizes results of relatively homogenous trials only. Generalization of study results significantly different by patient's characteristics, various aspects of using the compared medicinal products, assessment criteria of the studied outcome is considered illegal, as these differences increase the non-homogeneity (heterogeneity) of the generalized data and reduce the significance of conclusions.

SR can include the use of the statistical method generalizing the results of several primary trials as if this could be one large study and make a common statistical conclusion on its basis. The method is called meta-analysis. United trials provide for a larger sample for analysis and greater statistical power. This increases exactness of assessing the effect of the analyzed intervention and improves substantiation of systematic review data with metanalysis as compared to separate experimental or descriptive trials.

The metanalysis can detect the effect failed to be detected during other experiments due to insufficient statistical power (a small number of participants in every experiment), it also enables a general conclusion based on several trials with various and even contradicting results [26, 27].

In spite of all advantages, meta-analysis is also not free from the effect of systematic errors and can contain false conclusions. It includes systematic errors such as errors of inclusion into SR and publication bias [28].

Inclusion errors reflect a low quality of systematic review. It is known that quality of meta-analysis significantly depends on quality of included initial trials and articles, i. e., on quality of the systematic review it is based on. The meta-analysis carried systematic errors of all primary works it consists of. When the published scientific literature reflects false assertions, meta-analysis also confirms false results.

Publication bias occurs when certain conducted stud trials without statistically significant differences in results between the groups of comparison or with results not different from the known data remained unpublished and weren't included into the meta-analysis. Then proportion of publications with positive results exceeds the real value resulting in overestimation of the averaged effect.

Disturbed methodology of SR is an insufficiently complete search of data, non-compliance with strict selection criteria and inclusion of low-quality trials leads to accumulation of systematic errors and reduces the veracity of SR results. Thus, a large high-quality RCT can provide more reliable results as compared with meta-analysis of some small ones.

Thus, systematic reviews and high-quality meta-analysis form the basis of evidence-based medicine analytical base and a very valuable tool while taking decisions about the choice of the most effective and safe methods of treatment and prevention.

HIERARCHY OF EVIDENCE OBTAINED IN CLINICAL TRIALS

Results of CT with various designs are currently used to develop clinical recommendations on prevention, diagnostics, treatment and rehabilitation. To understand the relative force of their substantiation, a hierarchy of evidence defined as ranking of CT with various designs by the degree of their liability to systematic errors was suggested [29]. At the top of the hierarchy, a method with the largest freedom from the systematic bias is located. It means that the true effect is close to the one obtained in the trial. At the lowest level of the hierarchy are types of trials not free from many systematic errors, which significantly reduces confidence in truthfulness of the obtained results.

Classification of the levels of evidence with some differences in CT assessment protocols are developed and utilized in various countries and large medical organizations. In the Russian Federation, the evidence levels of CT included into clinical recommendations are assessed based on the results of one or several CT of the highest rank in accordance with a single scale along with requirements approved by the order of the Ministry of Health of the Russian Federation as of Febr. 28, 2019 Np. 103н.

Level of evidence (LE) is a level of confidence indicating that the found effect related to the medical intervention is true [30]. Five levels of evidence reliability are provided (table 1).

Recommendations made using CT results are also ranged based on the **evidence level** (EL), which is determined as the rate of confidence in validity of the intervention effect and that following recommendations will do more good than it does harm.

The evidence level is determined based on assessment of methodological quality of CT, consistency of results of CT used to assess the EL, and importance of outcomes.

Methodological quality of CT is estimated using the respective point questionaries developed separately for SR, RCT, cohort trials and case-control trials. The CT results are considered as agreed if all the CT have effects of the same direction and if, as a consequence, the same conclusions are made. It means that there is an advantage of intervention A over

Table 1. Scale for determining the levels of evidence (LE) for therapeutic, rehabilitation and preventive interventions

LE	Hierarchy of designs of clinical trials (in descending order of the evidence level from 1 to 5)
1	Systematic review of RCT using meta-analysis
2	Other RCT and systematic reviews of trials of any design (except for RCT using meta-analysis)
3	Non-randomized comparative trials, including cohort ones
4	Non-comparative trials, description of a clinical case or set of cases, a case-control trial
5	Preclinical studies (substantiating the mechanism of action for this intervention) or experts' opinion

Table 2. Scale determining the evidence strength levels

LE	*Interpretation*
A	**Strong recommendation** (simultaneous fulfillment of two conditions): • all considered criteria of effectiveness (outcomes) are important, • all trials are of high or satisfactory methodological quality, • their conclusions on interesting outcomes are agreed
B	**Conditional recommendation** (if at least one condition is met): • not all considered effectiveness criteria (outcomes) are important, • not all trials have a high or satisfactory methodological quality, • their conclusions on interesting outcomes are not agreed
C	**Weak recommendation** means a lack of evidence of proper quality (if at least one condition is met): • all considered criteria of effectiveness (outcomes) are not important, • all trials are of low methodological quality, • their conclusions on interesting outcomes are not agreed

intervention B in all CT with a higher design [31]. Based on CT results, importance (significance) of outcomes is determined as important and not important. Important outcomes include all clinical outcomes ('solid end points'), surrogate outcomes estimated by validated scales, surrogate outcomes with proven associated clinical outcomes based on CT results.

Not important outcomes include surrogate outcomes in the lack of CT that confirm association with clinical outcomes ('solid end points'). These are values of non-validated clinical scales, laboratory values, subjective assessments of patients (including using the visual analogue scales), and duration of symptoms.

Assessment of the level of evidence of recommendations for diagnostic, therapeutic and preventive interventions and rehabilitation activities is also carried out in accordance with a single scale and requirements approved by order of the Ministry of Health of Russia as of February 28, 2019 No. 103н. As far as evidence goes, there are strong, conditional and weak recommendations denoted using Latin letters A, B, C (table 2).

Proper assessment of evidence levels of recommendations and levels of confidence of CT, on which recommendations are based, should ensure their high scientific validity, which corresponds to requirements of medicine based on evidence.

CONCLUSIONS

Various clinical epidemiological trials intended to achieve different purposes and tasks are applied as a tool to obtain new knowledge in the field of medicine. CT differ by their structure and exactness used to estimate the cause-and-effect relations between the phenomena. Thus, while estimating accuracy of these conclusions, we need to be patient about the limitations typical of various designs. Exactness of CT depends on many factors, which can distort the obtained results as compared with their true values. The influence of these factors (systematic and accidental errors) enables to make alternative conclusions about the reasons for the discovered differences.

Designs of various CT admit the influence of a greater or a smaller number of these factors. It is reflected on the reliability of results of CT. Neither study is free from systematic and accidental errors. However, observational trials are subject to them to a greater extent than experimental ones. This is explained by the fact that due to design characteristics observational trials can't be used to control errors associated with the possible non-correspondence of comparison groups. They can be used to detect a statistical relation between the phenomena but only RCT can prove that this is about a causal relation. Exactness of RCT can be increased with systematic reviews and meta-analyses.

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ETHICAL ISSUES OF THE OFF-LABEL USE OF DRUGS FOR TREATMENT OF COVID-19

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The article discusses the issues related to the ethical aspects of the off-label use of medications for treatment of coronavirus infection, including in terms of conducting clinical trials of these medications. Furthermore, the article raises the issue of using drugs for treatment of coronavirus infection at the moment and discusses the related ethical principles. The major issue of this review is the ethical aspect of the search for benefits of using drugs not according to instructions in patients with emergencies and life-threatening conditions, such as COVID-19. The ethical role of the informed consent in both clinical trials and off-label prescription of drugs in general is also clarified. Several options provided in this review are proposed to address this issue.

Keywords: off-label, COVID-19, coronavirus infection, use not according to instructions, medical ethics

Author contribution: Severova YaG developed the concept and the structure of the article, reviewed the literature and wrote the text; Teplova NV contributed to the article concept development, provided academic supervision, finalized the text and approved it before publishing.

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ЭТИЧЕСКИЕ ВОПРОСЫ OFF-LABEL ПРИМЕНЕНИЯ ПРЕПАРАТОВ ДЛЯ ЛЕЧЕНИЯ COVID-19

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В статье рассматриваются вопросы, касающиеся этической стороны применения off-label препаратов для лечения коронавирусной инфекции, в том числе и в ключе проведения клинических исследований с данными лекарственными средствами. Помимо этого в данной работе затронут вопрос применения лекарственных препаратов для лечения коронавирусной инфекции в настоящее время и связанные с этим этические принципы. Основная проблема данного обзора заключается в этическом вопросе поиска пользы применения препаратов не по инструкции при экстренных и жизнеугрожающих состояниях, таких как COVID-19. Также уточняется этическая роль добровольного информированного согласия как на проведение клинических исследований, так и в целом на назначение off-label препаратов. Для решения данной проблемы было предложено несколько вариантов, представленных в данном обзоре.

Ключевые слова: off-label, COVID-19, коронавирусная инфекция, применение не по инструкции, медицинская этика

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Coronavirus infection is a dangerous rapidly developing and spreading infection that has caused one of the world's greatest pandemics. As of September 2022, a total of 20,535,057 COVID-19 infection cases have been reported in the Russian Federation. This amounts to 3.32% of the total number of infected people, and the disease lethality is 1.88% [1].

The lack of efficient medications for treatment and prevention of coronavirus infection was an important public health problem soon after the emergence of COVID-19, which resulted in the active off-label use of drugs (i. e. not according to instructions). Drug therapy of coronavirus infection was based not on the empirical evidence of clinical trials (CT), but on the physicians' assumptions. The major issue associated with prescription and use of drugs not according to instructions (off-label use) is as follows: despite the fact that the health risks of these drugs (based on the use in accordance with the confirmed indications) are generally predictable, the efficiency of their use according to the new indications, i. e. for treatment of COVID-19, was not predictable and provided nothing close to evidence in terms of efficacy and safety. While it was natural that the off-label use meant primarily gaining the benefits in the form of beneficial therapeutic effect for the patient. That is why the study was aimed to review the legal and ethical aspects of the off-label drug use, clinical trials of the off-label drug use for treatment of coronavirus infection, and the ways of addressing issues associated with the use of drugs not according to instructions.

LEGAL AND ETHICAL ASPECTS OF THE USE OF DRUGS FOR TREATMENT OF COVID-19 NOT ACCORDING TO INSTRUCTIONS

Today, according to the latest update of the guidelines on the coronavirus infection prevention and treatment and the guidelines issued by the World Health Organization (WHO), it is possible to prescribe drugs that are assumed to be efficient when used off-label for etiotropic therapy (i. e., the drug medical use does not meet the guidelines on medical use). However, the drugs must be prescribed in accordance with the ethical standards recommended by the WHO and based on Federal Law (FZ) No. 323-FZ, FZ No. 61-FZ, GOST R ISO 14155–2014 "Good Clinical Practice", the order of the Ministry of Health

(MH) of the Russian Federation (RF) No. 200n, and the World Medical Association (WMA) Declaration of Helsinki on the ethical principles of research involving human subjects declared during the 64th WMA General Assembly, Fortaleza, Brazil, 2013. [2]. According to the WHO, the off-label use of drugs is justified in cases of severe conditions when there is evidence of potential benefits, but there is no standard therapy, the patients are informed and have given consent (in writing wherever possible), and the patients are under supervision due to safety reasons [3]. However, it is worth emphasizing that in the RF the off-label use of drugs in children is allowed by the Federal Law No. 482 on Amendment to the Federal Law "On the Basics of Protecting the Health of Citizens in the Russian Federation", while the established list of disorders that includes COVID-19 is set out in the Decree of the Government of the Russian Federation No. 1180-R [4,5]. Based on this Law, the use of drugs not according to instructions within the legal framework is possible only in people under the age of 18. This contradicts the data of the guidelines on prevention and treatment of coronavirus infection. Anyway, parents must submit a written consent to make possible the off-label use of drugs in children. As for adults, based on legal precedents, physicians do not have an obligation to inform patients or their families about the unintended use, addition or replacement of the drug during treatment, since there is a chance this could affect the patient's decision [6]. However, the informed consent is a fundamental principle of medical law and ethics, that is why physicians must obtain the patient's consent prior to treatment. It is worth noting that in terms of ethics the off-label use of drugs for treatment of coronavirus infection without the results of CTs should be considered only in cases of emergencies and life-threatening conditions when there is no effective evidence-based treatment; when the informed consent is available; when all treatment stages are documented. Active cooperation with the Federal Service for Surveillance in Healthcare in terms of pharmacovigilance should be also taken into account.

ETHICAL ISSUES OF CONDUCTING CLINICAL TRIALS OF THE OFF-LABEL USE OF DRUGS FOR TREATMENT OF CORONAVIRUS INFECTION

To conduct the CT of the off-label drug use, it is necessary to consider certain ethical and scientific principles, ethical guidelines and ethical approval even in case of unexpected dangerous outbreak, such as COVID-19 outbreak. In the RF, the MH issued the letter explaining how to conduct CTs during the COVID-19 pandemic. According to the letter, it may be difficult to perform the procedures of the CT protocols due to challenging current situation. In such cases the drug CT managers together with the researchers and local ethics committees can adjust standard operating procedures on behalf of the CT participants taking into account the guarantees of data reliability [7]. Thus, in the RF favipiravir was registered in accordance with the registration procedure for drugs intended for use in the context of threat of emergency situation or emergency response, but about it a little later.

Of course, the MH places a priority on the CT participants' safety and reasonable risk-benefit balance for research subjects. The MH recommends the CT managers to consider alternative possibilities of conducting CT, such as shifting to online monitoring methods (virtual visits, telephone conversations, etc.), home delivery of medications, careful documentation of all anomalies, protection of personnel involved.

Thus, when discussing the ethical issue of conducting CTs of the off-label use of drugs for treatment of coronavirus infection, several example are worth mentioning. For example, in the CTs of hydroxychloroquine treatment resulted in no beneficial clinical effects, while the rate of side effects was almost twice larger compared to placebo. In these cases, patients in the treatment group had a high risk of suffering from the harmful effects of the drug and would have got minimum benefits when using this drug [8]. In contrast, another group of patients enrolled in other CTs, such as the CT of remdesivir, recovered faster and showed fewer side effects [9]. Such situation in the group, receiving, for example, hydroxychloroquine, would be a "lost opportunity" in contrast to participants of other CTs showing more beneficial results. The other problem is that in some cases patients with severe and critical conditions admitted to the intensive care unit are unable to give a verbal consent or have very little time to give the consent. In such cases the consent given by relatives or legal representatives does not always correspond to the patient's desire. Thus, to address the ethical issues related to the CTs of the off-label use of drugs for treatment of COVID-19, it is necessary to implement the adaptive research planning model, i. e., the study of several medications within the framework of one CT. This would make it possible to transition all groups to the more efficient and safer drug. Furthermore, the more precise legislative regulation of CTs is required withing the framework of consent or refusal of participation in cases of pandemics and life-threatening conditions.

PRESENT-DAY ETHICAL ISSUES OF TREATING CORONAVIRUS INFECTION

As has become clear from the above, there were no data on the effective and safe treatment confirmed by CTs in the beginning of the COVID-19 pandemic, that is why the medical community had to rely on their own clinical experience and prescribe drugs off-label. However, after more than two years since the beginning of the pandemic, the clinical and epidemiological features of the disease are intensively studied, and the new means for prevention and treatment of coronavirus infection are developed. Today, according to the guidelines issued by MH of the RF, etiotropic therapy is used along with the pathogenetic and symptomatic therapy. There are several drugs that could be used for treatment of COVID-19: favipiravir, molnupiravir, nirmatrelvir + ritonavir, remdesivir, synthetic small interfering ribonucleic acid (siRNA) [double-stranded], umifenovir and interferon-alpha [2].

However, in terms of evidence-based medicine, the drugs recommended by the MH of the RF at least cannot be considered effective, despite the fact that these are not used off-label. To prove his statement, the randomized double-blind multicenter placebo-controlled CTs of favipiravir were reviewed. The study results showed no decrease in the time till viral clearance or showed just a non-significant trend toward the increase in viral clearance along with no significant therapeutic benefits. The independent data and safety monitoring board (DSMB) recommended to withdraw the drug due to futility of interim analysis [10, 11]. According to the Directory of Medicines, the instructions to favipiravir have been developed based on the limited clinical data on the drug use and would be amended as new data become available [12]. It is worth noting that the drug is used according to instructions in hospital settings, but there are many cases of prescribing favipiravir in outpatient settings, which means favipiravir is used not according to instructions. In this way, even if we consider this drug as relatively safe, the data of CTs show it is inefficient, and it is questionable whether the use of this drug is feasible from the ethical and medical point of view. Despite the fact that the

drug is included in the guidelines on treatment of coronavirus infection and is not an off-label drug, the use of this medication cannot be considered reliable.

CONCLUSION

In conclusion, it should be noted that prescription of drugs not according to instructions or during clinical trials is considered unethical unless proven otherwise. However, it is worth mentioning that in the context of the pandemic the ideas about the off-label prescription of drugs could be revised due to emergency and lack of evidence-based treatment. To adhere to ethical standards, it is necessary to improve the legislative framework of the off-label use of drugs an implement the adaptive CT model. Furthermore, it is necessary to think critically about the existing guidelines on treatment and prevention of coronavirus infection.

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ETHICAL ASPECTS OF THE QUALITY OF LIFE IN PATIENTS WITH ATHEROSCLEROSIS

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The concept of quality of life is an integral characteristic of human physical, psychological, emotional, and social functioning. The disorders associated with atherosclerosis reduce the patients' quality of life. Surgical treatment improves physical health of patients with atherosclerosis affecting primarily precranial arteries. The decrease in the indicators of physical functioning, role-playing, and bodily pain in patients with atherosclerosis mostly affecting the arteries of lower extremities persists in the late postoperative period. Comprehensive analysis of the broad spectrum of factors, such as clinical and demographic, anatomic, laboratory and instrumental, medical and social, and psychological factors, is the key to successful revascularization associated with the lowest risk of possible adverse events that makes it possible to implement the personalized approach to treatment and rehabilitation of patients. Ethical regulation of the quality of life assessment by the patient, his/her relatives and medical professionals is required. Reconciling the positions of the parties on the issue requires bioethical expertise in studying indicators of the quality of life.

Keywords: atherosclerosis, surgical treatment, quality of life

Author contribution: Volkova AS — analysis of the research data, review of publications on the topic of the article, summary, manuscript writing; Ilyin MV — developing the article design, statistical analysis, manuscript editing; Kagramanyan IN — consultations on the issues related to the study, literary editing of the article, scientific editing of the article; Khokhlov AL — consultations on the issues related to the study, literary editing, scientific editing of the article.

Compliance with ethical standards: the study was approved by the Ethics Committee of the Yaroslavl State Medical University. The informed consent was submitted by all subjects. The survey of adults was performed on a voluntary basis.

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ЭТИЧЕСКИЕ АСПЕКТЫ КАЧЕСТВА ЖИЗНИ БОЛЬНЫХ АТЕРОСКЛЕРОЗОМ

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Понятие качества жизни представляет собой интегральную характеристику физического, психологического, эмоционального и социального функционирования человека. Заболевания, ассоциированные с атеросклерозом, снижают качество жизни пациентов. Хирургическое лечение приводит к улучшению физического здоровья больных атеросклерозом с преимущественным поражением прекраниальных артерий. Снижение показателей физического функционирования, ролевой деятельности и телесной боли у больных атеросклерозом с преимущественным поражением артерий нижних конечностей сохраняется также в отдаленном послеоперационном периоде. Главным залогом успешной реваскуляризации, ассоциированной с наименьшим риском возможных неблагоприятных событий, является комплексный анализ широкого спектра факторов, включая клинико-демографические, анатомические, лабораторно-инструментальные, медико-социальные и психологические, что позволяет реализовать персонифицированный подход в лечении и реабилитации пациента. При оценке качества жизни самим пациентом, его родственниками и медицинскими работниками необходима этическая регуляция. Согласование позиций сторон в данном вопросе требует проведения биоэтической экспертизы в исследовании показателей качества жизни.

Ключевые слова: атеросклероз, хирургическое лечение, качество жизни

Вклад авторов: А. С. Волкова — анализ научного материала, обзор публикаций по теме статьи, составление резюме, написание текста статьи; М. В. Ильин — разработка дизайна статьи, статистические расчеты, редактирование статьи; И. Н. Каграманян — консультирование по вопросам проведения исследования, литературное редактирование статьи, научное редактирование статьи; А. Л. Хохлов — консультирование по вопросам проведения исследования, литературное редактирование, научное редактирование статьи.

Соблюдение этических стандартов: данное исследование было одобрено Этическим комитетом ФГБОУ ВО ЯГМУ Минздрава России. Добровольное информированное согласие было получено для каждого участника. Обследование для взрослого населения проводилось на добровольной основе.

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Quality of life is an essential aspect of bioethics. Surgical interventions aimed at improving the patient's quality of life sometimes raise serious ethical issues that emerge in case of conflict between the patient's preferences associated with his/her perceptions of the quality of life and the limitations associated with the disease. Manifestations of atherosclerosis have a major impact on the patients' quality of life. Reduced quality of life in patients with atherosclerosis obliterans of the lower extremities results from the limitation of physical exertion, mostly walking, and intensity of the pain syndrome [1]. In patients with carotid stenosis, the quality of life is usually assessed in conjunction with the assessment of cognitive impairment. Psychopathological disorders associated with vascular disease are also related to the psychological reaction to illness [2].

The patient's quality of life is a subjective indicator that reflects a broad spectrum of parameters related to physical activity, capability of labour, social interactions, and self-care, as well as to emotional stability, the presence or absence of discomfort, including feeling uncomfortable due to illness [3]. Furthermore, estimation of the quality of life is used as an independent criterion of treatment efficiency [4, 5].

The questionnaire method is used to assess the patients' overall satisfaction with their quality of life. The SF-36 Health Status Survey (SF-36) designed for assessment of overall well-being in both physical and psychoemotional spheres is one of the model questionnaires. The advantages of the questionnaire are the comprehensive nature and non-specificity, i. e. suitability for assessment of the parameters associated with various disorders.

The study was aimed to assess the indicators of the quality of life in patients with atherosclerosis who were referred for surgery.

METHODS

The study involved 47 patients with atherosclerosis, among them 25 (53.2%) patients with atherosclerosis of precranial arteries and 22 (46.8%) patients with atherosclerosis obliterans of the lower extremities, referred for surgery to the Department of Vascular Surgery of the Yaroslavl Regional Clinical Hospital. Study design: single-centre non-randomized open-label prospective parallel group study. The endpoints were assessed six months after the patient enrollment.

The clinical status and quality of life in patients with atherosclerosis were assessed based on the completed SF-36 questionnaire. The questionnaire reflects the patient's conditions according to the following scales: physical functioning (PF), role-playing (RP), bodily pain (BP), general health (GH), viability (VT), social functioning (SF), emotional state (RE), and mental health (MH). The scores of all scales vary between 0 and 100, where 100 corresponds to full health. The changes in the indicators over time reflect the dynamic changes in the clinical status, including those resulting from treatment.

Statistical data processing was performed using the STATISTICA 10.0 software package (StatSoft Inc., USA). The distribution of quantitative traits was tested for normality using the Lilliefors corrected Kolmogorov–Smirnov test and Shapiro–Wilk test. The data were presented as median and percentiles due to non-normal distribution. The Wilcoxon test was used to compare two independent groups by one trait. The critical level of statistical significance was within 5.0%.

RESULTS

The assessment of the quality of life in patients with atherosclerosis on admission to the hospital for surgical treatment showed the following results (Fig. 1).

There were no significant differences ($p < 0.05$) in the indicators of general health (GH), social functioning (SF), emotional state (RE), and mental health (MH) in patients with atherosclerosis affecting mostly brachiocephalic arteries (BCA) and atherosclerosis obliterans of peripheral arteries (PA). The quality of life in patients with atherosclerosis of brachiocephalic arteries was higher based on the comparison of the indicators of physical functioning (PF), role-playing (RP), and bodily pain (BP). This was probably due to limited physical activity associated with severe pain syndrome in patients with atherosclerosis obliterans of the lower extremities.

The dynamic changes in the indicators of mental (MH) and physical (PH) health components in the general group of patients with atherosclerosis ($n = 47$) in the early postoperative period are provided in Table 1.

The data provided in Table 1 demonstrate a significant ($p = 0.004$) improvement of physical health in patients with atherosclerosis after vascular reconstruction.

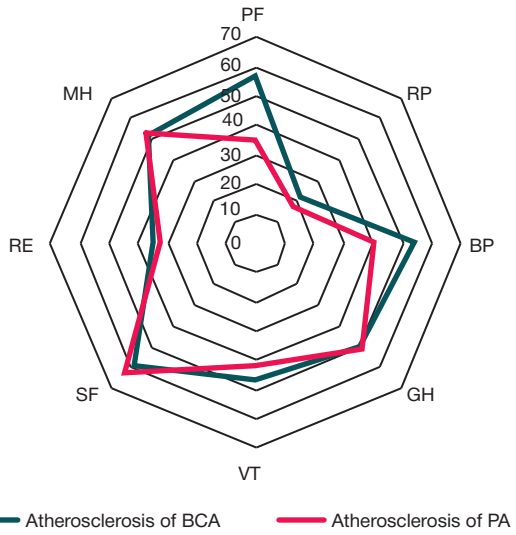

Fig. 1. Assessment of the quality of life in patients with atherosclerosis on admission to the hospital

Table 1. Dynamic changes in the indicators of mental (MH) and physical (PH) health components in patients with atherosclerosis (n = 47)

Indicator	Before surgery	After surgery	*p*
MH, points	39.5 (34.3; 44.8)	39.9 (33.7; 48.9)	0.98
PH, points	34.3 (28.5; 39.7)	36.1 (30.2; 45.4)	0.004

Table 2. Dynamic changes in the indicators of mental (MH) and physical (PH) health components in patients with atherosclerosis of BCA (n = 25)

Indicator	Before surgery	After surgery	*p*
MH, points	39.5 (34.3; 41.2)	37.7 (33.7; 46.8)	0.85
PH, points	38.1 (31.3; 44.9)	41.4 (32.1; 49.6)	0.015

Table 3. Dynamic changes in the indicators of mental (MH) and physical (PH) health components in patients with atherosclerosis of PA (n = 22)

Indicator	Before surgery	After surgery	*p*
MH, points	40.1 (34.3; 51.6)	40.6 (34.3; 51.6)	0.97
PH, points	33.1 (27.7; 35.3)	33.8 (27.7; 38.0)	0.11

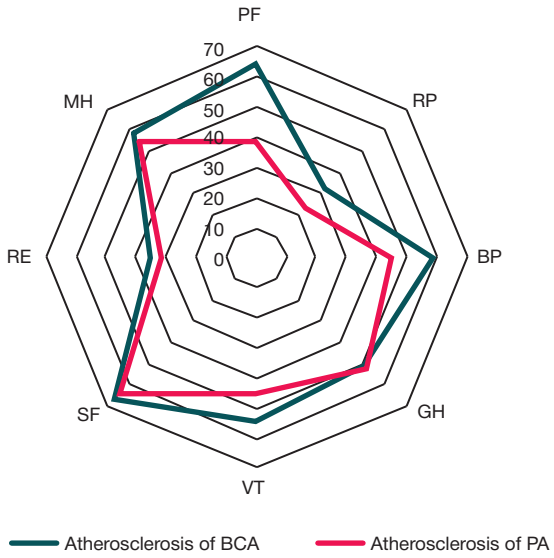

Fig. 2. Assessment of the quality of life in patients with atherosclerosis six months after surgery

The analysis of the dynamic changes in the indicators of MH and PH observed in patients with atherosclerosis affecting mostly brachiocephalic arteries that performed after surgery is provided in Table 2.

The patients with atherosclerosis of BCA demonstrate a significant (p = 0.015) improvement of the quality of life in the physical sphere during the postoperative period. No significant differences in the indicators of psycho-emotional health have been revealed in this group of patients.

The dynamic changes in the studied indicators in patients with atherosclerosis of PA are provided in Table 3.

Based on the data provided in Table 3, no significant differences in the indicators of physical and psycho-emotional health have been revealed in patients with atherosclerosis of PA during the postoperative period.

Thus, the increase in the indicators of physical (PH) health component observed in the general group of patients with atherosclerosis was entirely due to the improvement observed in the group of operated patients with atherosclerosis of brachiocephalic arteries.

Assessment of the quality of life in patients with atherosclerosis in the late postoperative period (six months after surgery) is provided in Fig. 2.

The characteristic pattern of the quality of life was maintained in patients with atherosclerosis six months after the vascular reconstruction surgery. The indicators of physical functioning (PF), role-playing (RP), and bodily pain (BP) in patients with atherosclerosis affecting mostly the arteries of lower extremities were still lower than those of patients with atherosclerosis of precranial arteries.

The disease affecting non-coronary artery systems adversely affects both physical and psychological components of the patients' quality of life. Arterial reconstruction results in the significant improvement of physical health in patients with atherosclerosis of precranial arteries. The decrease in the indicators of physical functioning (PF), role-playing (RP), and bodily pain (BP) observed in patients with atherosclerosis affecting mostly the arteries of lower extremities persists in the late postoperative period.

The comprehensive analysis of the broad spectrum of factors, such as clinical and demographic, anatomic, laboratory and instrumental, medical and social, and psychological factors, is the key to successful revascularization associated with the lowest risk of possible adverse events that makes in possible to implement the personalized approach to treatment and rehabilitation of patients. Ethical regulation of the quality of life assessment by the patient, his/her relative and medical professionals is required. Reconciling the positions of the parties on the issue requires bioethical expertise in studying indicators of the quality of life.

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CLINICAL, ECONOMICAL AND ETHICAL ASPECTS ASSESSING THERAPY OUTCOMES IN PATIENTS WITH MULTIPLE MYELOMAS OF HIGH CYTOGENETIC RISK

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According to European authors, patients with multiple myeloma (MM) and high cytogenetic risk have shorter values of progression free survival (PFS) and overall survival (OS) as compared with standard hazard. More frequent hospitalizations mean potentially high expenses associated with management of patients with unfavorable cytogenetic risk. Cost and availability of treatment of oncological patients relate to one of pressing ethical issues. Another important aspect of this issue consists in an effective use of available approved modes of therapy in patients with various survival prognosis, which is especially critical for early lines of therapy. It has been proven that early administration of more effective modes based on individual characteristics both of a patient, and a disease will improve the total survival of patients. This will result in reduction of economic resources spent on selecting new modes of treatment in patients with a disease recurrence and correction of possible adverse effects and hospitalization.

Key words: multiple myeloma, cytogenetic risk, clinical and economical assessment, ethical issues, overall survival, hospitalizations

Author contribution: Zabolotneva YA — collection, analysis and synthesis of data, writing the article; Gurevich KG — idea of and writing the article.

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КЛИНИКО-ЭКОНОМИЧЕСКИЕ И ЭТИЧЕСКИЕ АСПЕКТЫ ОЦЕНКИ ИСХОДОВ ТЕРАПИИ ПАЦИЕНТОВ С МНОЖЕСТВЕННОЙ МИЕЛОМОЙ ВЫСОКОГО ЦИТОГЕНЕТИЧЕСКОГО РИСКА

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По данным европейских авторов, у пациентов с множественной миеломой (ММ) с высоким цитогенетическим риском наблюдаются значительно более короткие значения беспрогрессивной (ВБП) и общей выживаемости (ОВ) по сравнению со стандартным риском. Более частые госпитализации указывают на потенциально высокие расходы, связанные с ведением пациентов с неблагоприятным цитогенетическим риском. Стоимость и доступность лечения онкологических пациентов являются одним из актуальных этических вопросов. Другой важный аспект этой проблемы это эффективное применение существующих одобренных схем терапии у пациентов с различным прогнозом по выживаемости, что особенно критично в ранних линиях терапии. Доказано, что назначение более эффективных режимов как можно раньше в соответствии с индивидуальными особенностями и пациента и заболевания будет способствовать увеличению в итоге общей выживаемости больных. Как результат позволит сократить экономические ресурсы, которые тратятся на выбор новых схем у пациента с рецидивом заболевания, а также на коррекцию возможных побочных эффектов, госпитализации.

Ключевые слова: множественная миелома, цитогенетический риск, клинико-экономическая оценка, этические вопросы, общая выживаемость

Вклад авторов: Ю. А. Заболотнева — сбор, анализ и синтез материала, написание статьи; К. Г. Гуревич — идея статьи, написание.

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Multiple myeloma (MM) is currently one of the most widely spread malignant vascular system tumors and, in spite of a significant number of accessible therapeutic options, patients' outcomes require improvement [1].

In patients with MM, various cytogenetic and molecular genetic breakages of tumor cells are met rather frequently and determined as the most important factors influencing the course and prognosis of MM (table 1) [2]. Depending on the effect produced on survival, high risk cytogenetic disturbances are detected (resulting in reduced overall survival) [1].

Determination of a high-risk myeloma has evolved over time and includes cytogenetic and clinical biomarkers (table 2) [3].

Due to a rather bad prognosis in a high-risk disease, there still remains a purpose of developing new treatment options for patients from a high-risk group. Thus, it's important to provide clear recommendations related to treatment of high-risk multiple myeloma to improve general therapy outcomes. The simplest approach to risk stratification is represented by the International Staging Scale that uses two available laboratory values (serum β2 microglobulin and serum albumin) (table 2) [3].

For a more exact prognosis, tumor load (stage) and disease biology (presence of molecular and genetic high-risk pathologies or increased level of LDH) should be assessed. The factors are estimated within the reviewed staging system (R-ISS) to develop a single prognostic index. To ensure consistency, only widely accepted cytogenetic markers such as trisomy, t (11;14), t (6;14), t (4;14), t (14;16), t (14;20), del 17p, + 1q are used in R-ISS [4]. The model of risk stratification called Mayo stratification (mSMART) and developed at Mayo clinic, which divides patients into two groups with high and standard risks, provides additional information for prognosis and selection of a therapeutic strategy (table 3) [5].

The prognostic value of (high-risk) cytogenetic abnormalities in MM is evident (table 4) [5, 6]. However, limited data of real practice (mainly of European origin) are currently available. They describe clinical and economical models of treatment and

Table 1. Incidence of various cytogenetic abnormalities (adapted by Abdallah et al. 2020) [2]

Cytogenetic abnormalities	N (tested patients)	N (%) with cytogenetic abnormalities
IgH translocation with trisomy	1959	312 (16)
t (11;14)	1962	58 (3)
t (4;14)	1961	60 (3)
t (14;16)	1961	23 (1)
t (6;14)	1962	9 (<1)
t (14;20)	1962	6 (<1)
Unknown deletion of IgH	1959	156 (8)
IgH translocation without trisomy	1959	581 (30)
t (11;14)	1962	315 (16)
t (4;14)	1961	117 (6)
t (14;16)	1961	55 (3)
t (6;14)	1962	9 (<1)
t (14;20)	1962	14 (<1)
Unknown deletion of IgH	1959	71 (4)
Trisomy without IgH translocation	1959	791 (40)

Table 2. MM staging based on ISS and R-ISS (adapted by Palumbo A et al. J Clin Oncol. 2015;33(26):2863–2869.) [3]

R-ISS	stage I	stage II	stage III
ISS	Serum β_2-microglobulin <3.5 mg/l; albumin ≥3.5 g/dl)	Not R-ISS stages I or III	Serum β_2- microglobulin ≥5.5 mg/l)
Cytogenetic disturbances (CD)	Standard risk*		High risk of CD** or high LDH (<above the normal interval)
LDH	Normal (<above the normal interval)		
	5-year OS (%)		
	82%†	62%†	40%†

* Lack of del(17p) mutation and/or t(4;14)(p16;q32) translocation and/or t(14;16)(q32;q23) translocation.
** Presence of del(17p) and/or t(4;14)(p16;q32) translocation and/or t(14;16)(q32;q23) translocation.
† In general population of 4445 patients with a mean age of 62 years, 60% received auto-HSCT (the majority were ≤65), 44% obtained proteosome inhibitors, 66% received immunomodulators, 5% obtained no novel agents. 871 patients developed (28%) R-ISS stage I, 295 (10%) R-ISS stage III, and 1894 (62%) R-ISS stage II.

Table 3. Classification of mSMART in MM [4]

Risk group	Stratification criteria	Treatment approaches
High	– High risk genetic abnormalities t(4;14) t(14;16) t(14;20) Del 17p p53 mutation + 1q R ISS stage 3 – High amount of plasma cells in S-phase (synthesis) – Gene expression profile (GEP): high risk	– Aggressive and continuous therapy – Triple-combination
Standard	All the rest including: – trisomy – t(11;14)[d] – t(6;14)	– Treatment-free intervals can be useful to get a minimal number of toxic therapy effects. – Triple combined therapy is preferable.

Adapted from mSMART Mayo Stratification for Myeloma and Risk-adapted Therapy Newly Diagnosed Myeloma. V14. Accessed January 24, 2019. https://www.msmart.org/mm-treatment-guidelines.

outcomes for patients with MM with high cytogenetic risk. Results of international randomized clinical trials presenting effectiveness of novel agents and their combinations in patients with different cytogenetic risks are published (table 5) [7]. It is shown that some regimens are able to overcome the high cytogenetic risk and increase overall survival of patients with MM.

Results of retrospective analysis of 200 patients with MM recurrence risk in France have been published [8]. Outcomes of patients during second-line therapy were estimated after the first recurrence. 192 patients (96%) obtained second-line therapy following the recurrence: the most widely used regimens included lenalidomide (>50%). The rate of hospitalization was approximately twice higher among patients with high risk as compared with patients with standard risk. Based on Kaplan-Meier estimator, median (95% CI) of second-line progression-free survival (PFS) was 21.4 (17.5, 25.0) months

Table 4. Comparison of tests using ISS and FISH-based prognostic models [5, 6]

	IMWG	MRC	Немецкое исследование
Treatment	Includes both young (transplant candidates) and elderly patients (chemotherapy only)	Young (intensive) and older patients (non-intensive) with thalidomide-based combination at induction and thalidomide maintenance on MRC IX trials	Chemo-based induction followed by HD Mel ASCT and maintenance
N	2637	629	315
Low risk			
Parameter	ISS* I/II, no adverse FISH abnormalities†	ISS I/II, no adverse FISH abnormalities‡; ISS I, 1 adverse FISH abnormality	ISS I, no adverse FISH abnormalities†
% of patients	51%	38%	42%
OS	76% during 4 years	Median of 67.8 months	72% during 5 years
Intermediate risk			
Parameter	ISS III, no adverse FISH abnormalities; ISS I, t(4;14)/del(17p13)	ISS I, >1 adverse FISH abnormality; ISS II/III, 1 adverse FISH abnormality; ISS III, no adverse FISH abnormalities	ISS II/III, no adverse FISH abnormalities; ISS I, t(4;14)/del(17p13)
% of patients	29%	48%	44%
OS	45% during 4 years	Median of 41.3 months	62% during 5 years
High risk			
Parameter	ISS II/III, t(4;14)/del(17p13)	ISS II/III, >1 adverse FISH abnormalities	ISS II/III, t(4;14)/del(17p13)
% of patients	20%	14%	14%
OS	33% during 4 years	Median of 19.4 months	41% during 5 years

* ISS stage I, β2-microglobulin <3.5 mg/l and albumin ≥3.5 g/dl; ISS stage III, β2-microglobulin ×5.5 mg/l; ISS stage II, not ISS or ISS III.
† Adverse FISH displacement t(4;14) and/or del(17p13).
‡ Adverse FISH adverse IgH translocation [t(4;14) or t(14;16) or t(14;20)], del(17p13), and/or 1q2

Table 5. Outcomes for patients depending on cytogenetic risk in newly detected MM (adapted by Caro J. et al. 2021) [7]

Test	Regimen	Design	Examined risk	Number of patients with high risk	Primary outcome measure	Results
SWOG-1211[21]	Elotuzumab-VRd vs VRd	Phase II, high risk only, not auto-HSCT candidates	Expression of high risk genes, t(14;16), t(14;20), del (17p), amp (1q21), high levels of LDH, PCL	100 (100)	PFS	31.5 vs 33.6 months p=0.45
SWOG S077[22,23]	VRd vs Rd	Phase III, not auto-HSCT candidates	t(4;14), t(14;16), del (17p)	44 (8)	PFS	38 vs 16 months P=0.19
ALCYONE[24]	Dara-VMP vs VMP	Phase III, not auto-HSCT candidates	t(4;14), t(14;16), del (17p)	98 (14)	PFS	18 vs 18.1 (not significant)
MAIA[25]	Dara-Rd vs Rd	Phase III, not auto-HSCT candidates	t(4;14), t(14;16), del (17p)	92 (12)	PFS	Not assessed, not significant
CASSIOPEIA[26]	Dara-VTd vs VTd	Phase III, auto-HSCT candidates	t(4;14), del (17p)	168 (15)	sCR in 100 days after auto-HSCT	24% vs 28%, not significant
GRIFFIN[27]	Dara-VRd vs VRd	Phase III, auto-HSCT candidates	t(4;14), t(14;16), del (17p)	30 (14)	sCR after consolidation	18,8% vs 30,8%, not significant
STAMINA[28,29]	Ауто-ТГСК +Rd supportive + VRd consolidation+Rd supportive vs tandem auto-HSCT +Rd supportive.	Phase III, auto-HSCT candidates	в2>5,5 mg/l, t(4;14), t(14;16), del (17p), t (14,20), del (13) or aneuploidy	223(29)	sCR in 38 months	57,6% vs 61,6% vs 62,9%, p not available value
EMN 02/H095[30,31]	VCD, VMP vs auto-HSCT (solitary or double)	Phase III, auto-HSCT candidates	t(4;14), t(14;16), del (17p)	225 (19)	sCR	20,3 vs 37,3 months, HR 0,63 (95CI, 046–0,88)

Abbreviations: VRd, bortezomib, lenalidomide, dexamethasone; PCL, plasma cell leukemia; LDH — lactate dehydrogenase; PFS, progression-free survival; Rd lenalidomide, dexamethasone; Dara, daratumumab; VMP, bortezomib, melphalan, prednisolone; VTd, bortezomib, thalidomide, dexamethasone; sCR, stringent complete response; auto-HSCT — autologous stem cell transplantation, в2 — beta-2 microglobulin; VCD — bortezomib, cyclophosphamide, dexamethasone; HR — hazard ratio

(as compared with standard risk: 10.6 [6.4, 17,0] vs 28.7 [22.1, 37.3] months). Median of second-line overall survival (OS) was 59.4 (38.8, NE) months (high risk as compared with standard one: 36.5 [17.4, 50.6] vs 73.6 [66.5, NE] months).

Among patients who initiated second-line treatment with bortezomib, third-line therapy with lenalidomide was the most widely spread regimen. Relatively small number of patients received bortezomib during third-line therapy after withdrawal of lenalidomide during the second-line therapy. The majority of patients cancelled treatment (*n* = 176.92%) by the moment when the study was completed. The principal reasons were disease progression (37%), lack of maximum response without expected additional profit (33%), and loss of response (13%). Duration of second-line treatment is commonly less than one year. It displays not satisfactory results for this line of therapy and requires to select a therapy regimen for every separate patient considering cytogenetic risk, starting from first-line therapy.

Thus, patients with high cytogenic risk had shorter values of PFS and OS as compared with standard one. More frequent hospitalization meant potentially high expenses associated with management of patients with high genetic risk. The data show that systemic collection and analysis of results obtained during the Russian real clinical practice of treatment of patients with MM are necessary for subsequent clinical and economical assessment of therapy outcomes in patients with high cytogenic risk of MM recurrence and possible correction of first-line treatment regimens.

Multiple myeloma is an incurable disease. Implementation of novel drugs into practice resulted in a significantly improved survival in the presence of multiple myeloma. This is associated with implementation of novel agents (proteasome inhibitors such as carfilzomib and ixazomib; monoclonal antibodies such as daratumumab and elotuzumab) into clinical practice [9–13]. In addition to new regimens, regimens with two medicinal agents used within a limited period of time, are increasingly replaced with regimens consisting of three or four medicinal preparations continuously used until progression. This improves survival even more [14]. Within 5 years, expected survival almost doubled from 38% in 1989–2000 to 64% in 2008–2016.

Some novel drugs and their combinations display high effectiveness in patients with high cytogenetic risk. However, a lack of recommendations regarding different therapy regimens depending on cytogenetic risk is a serious problem both for doctors, and for patients with myeloma.

Implementation of novel agents and improved overall survival result in higher expenses on treatment of oncological patients [15, 16].

The growing expenses are only partially associated with the incidence rate [17]. As compared with medicinal agents used for other indications, oncological drugs are more costly in absolute and relative terms [18]. These growing expenses cause concern as they compromise availability of effective therapy for patients.

For instance, among patients newly diagnosed with MM in the USA, healthcare expenditure per one patient a month increased from 3,263 US dollars in 2000 to 14,656 US dollars in 2014 [19].

Clinical and economical aspects of treatment of patients with MM raise a number of ethical questions. Cost of therapy is one of them. Providing treatment to people with limited resources forms the basis of any healthcare system. Growing worldwide cost of drug therapy of oncological diseases combined with insufficiently effective therapy outcomes raise questions about how effectively the existing therapy regimens are used in patients with different survival prognosis. This is especially true for early therapy lines because administration of more effective regimens based on individual characteristics both of the patient, and the disease, will sooner or later contribute to increased overall survival of patients. In future, this will reduce economical resources spent on selection of new regimens for a patient with disease recurrence, and correction of possible adverse effects and hospitalization.

For instance, the mean assumed threshold of economical effectiveness among oncologists was 280,000 US dollars per quality-adjusted life year (QALY). It is much higher than 50,000 US dollars per QALY regularly used by healthcare experts [20]. At least one oncologist in this study noted that addition of one day of life would justify expenses in the amount of 70,000 US dollars per year which is equivalent to 25 mln US dollars per QALY.

At disease onset, assessment of prognostic factors (including pathogenetic risk) in a patient with MM should be of fundamental importance while selecting therapy and will ultimately promote better overall survival. It will reduce a number of hospitalizations and expenses on correction of adverse events. Implementation of novel agents into clinical practice and increased cost of management of patients with oncological diseases (including the ones with multiple myeloma) raise ethical issues of therapy availability and need of patients in the most effective regimens based on their individual and disease characteristics.

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MANAGEMENT AND TREATMENT OF A PATIENT WITH A HORMONALLY ACTIVE ADRENAL TUMOR

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In spite of all existing achievements, modern endocrinology comes across a rather complex issue such as treatment of patients with catecholamine secreting tumors. True prevalence of pheochromocytoma is not known, as data obtained during the research depend on criteria of patients' selection and can vary significantly. The tumors have numerous pathophysiological mechanisms of disease development due to a wide variability of symptoms and complex diagnostics. Meanwhile, timely diagnosis produces a direct effect on prognosis and quality of life. Catecholamine secreting tumors are commonly not detected. In such cases, there is a high risk of severe cardiovascular complications up to a lethal outcome. Complex diagnostics of this pathology also means that the tumors can have adrenal and extraadrenal localization and that the disease is hereditary. This makes diagnostics and treatment of pheochromocytoma even more complex. Timely detection of concomitant tumor and hormonal manifestations belongs to an important factor of management of patients with genetically determined pheochromocytomas. Thus, examination of pheochromocytoma is a pressing issue of modern endocrinology.

Keywords: pheochromocytoma, arterial hypertension, metanephrines and normetanephrines

Author contribution: Zhilina AN — patient management until the surgery, writing the article, summing up data of laboratory and instrumental diagnostics during the preoperative and postoperative stages; Melnikova JuE — MRI diagnostics with pheochromocytoma contrasting; Voronina EA — deciphering genetic research; Martyshova AV — literature review of modern data and recommendations regarding management of patients with this pathology.

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НАБЛЮДЕНИЕ И ЛЕЧЕНИЕ ПАЦИЕНТКИ С ГОРМОНАЛЬНО-АКТИВНОЙ ОПУХОЛЬЮ НАДПОЧЕЧНИКА

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Современная эндокринология, не смотря на все существующие достижения, сталкивается с довольно сложной проблемой — это лечение пациентов с опухолями, секретирующими катехоламины. Истинная распространенность феохромоцитомы неизвестна, так как данные, полученные в исследованиях, зависят от критериев подбора пациентов и могут значительно различаться. Данные опухоли характеризуются многообразием патофизиологических механизмов развития заболевания, что обусловливает широкую вариабельность симптоматики и сложности в диагностике. При этом своевременный диагноз непосредственно влияет на прогноз и качество жизни пациентов. Нередко опухоли, секретирующие катехоламины, остаются не выявленными, в таких случаях очень высок риск тяжелых сердечно-сосудистых осложнений вплоть до смертельного исхода. Сложность диагностики данного вида патологии заключается также и в том, что данные опухоли могут иметь надпочечниковую и вненадпочечниковую локализацию, а также наследственный характер заболевания, что еще больше добавляет сложностей в диагностике и лечении феохромоцитомы. Своевременное выявление сопутствующих опухолевых и гормональных проявлений является важным фактором в ведении пациентов с генетически-детерминированными феохромоцитомами. В связи со всем вышеперечисленным изучение феохромоцитомы является актуальной проблемой современной эндокринологии.

Ключевые слова: феохромоцитома, артериальная гипертензия, метанефрины и норметанефрины

Вклад авторов: А. Н. Жилина — ведение пациентки до оперативного лечения, написание данной статьи, суммирование всех данных лабораторной и инструментальной диагностики на дооперационном и послеоперационном этапах, Ю. Е. Мельникова — МРТ диагностика с контрастированием феохромоцитомы, Е. А. Воронина — расшифровка генетических исследований, А. В. Мартышова — литературный обзор современных сведений и рекомендаций по ведению пациентов с данной патологией.

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Pheochromocytoma is a tumor of the adrenal medulla composed of chromaffin cells that produce catecholamines (adrenalin, noradrenalin and dopamine). For the first time, it was mentioned in 1886 by Frankel, a German pathologist. He found it on autopsy in two adrenal glands of an 18-year-old woman who suddenly died from collapse. A variety of pathophysiological mechanisms of this disease caused by tumor produced hormones explains a wide variability of symptoms and difficulties in diagnostics.

Timely set diagnosis produces a direct effect on prognosis and quality of life [1]. Incidence of pheochromocytoma among patients with hypertension is 0.2–0.6%. Hereditary mutation is a reason for pheochromocytoma in at least one third of patients [2]. It is known that in the majority of cases pheochromocytoma produces large amounts of catecholamines, whereas a lack of therapy can result in cardiovascular diseases and cerebral catastrophes, even fatal [3]. An increasing tumor can lead to compression syndrome [4]. Detection of pheochromocytoma as part of hereditary syndromes can be the reason for timely diagnostics and treatment of other members of proband family. Incidence of malignant pheochromocytoma is 10–17%. Its malignancy can be determined not just using

standard morphological and immunohistochemical criteria, but also by presence of metastases in non-chromaffin tissue. Pheochromocytoma is malignant in over 40% of observations in case of mutations in a gene that encodes succinate dehydrogenase complex subunit B (SDH-B) [5].

CLINICAL CASE

Patient K, 38 y. o., went to see an endocrinologist at the Lokomotiv Center for Sports Medicine on December 15, 20. She complained of crisis increase of BP to 220 mm Hg (systolic) accompanied by a fear of death, tachycardia up to 120 beats per minute, tremor in the body, pulsating headache in the occipital area, tingling and burning sensation in the fingers, sudden reddening of the face prior to an increase in BP. The increase in BP was noted at least 4–5 times a day. Such an increase was stopped in approximately 30 minutes after taking 40 mg of propranolol. The decrease in BP was accompanied by involuntary release of a large amount of light urine, cold sticky sweat, and pressing sensation behind the sternum without irradiation.

Anamnesis morbi: first complaints of increased BP to 220 mm Hg occurred in January 2020. They were developed due to emotional overload, leaving a room and going to the cold air and physical loads (skiing). The patient referred to a cardiologist numerous times and was diagnosed with stage 3, grade 2, risk 3 hypertension, antihypertensive therapy with various combinations of medicinal agents (bisoprolol 10 mg + perindopril 10 mg + moxonidine 0.6 mg; bisoprolol 10 mg + azilsartan + chlorthalidone; amlodopine 10 mg + bisoprolol 10 mg + hypothiazid 25 mg) was provided. None of the provided antihypertensive treatment option failed to prevent hypertensive crisis. In April 2020, the patient was recommended to refer to an endocrinologist. Due to a complex epidemiological situation associated with COVID pandemics and unavailable planned aid of narrow specialists, the patient managed to consult an endocrinologist only in December 2020. Until that time, she used previously suggested antihypertensive agents without a positive effect trying to stop hypertensive crises with propranolol. However, the abovementioned attacks were observed even more frequently, and the patient's well-being worsened.

Anamnesis vitae: concomitant diseases: 1 grade obesity; 2B dyslipidemia, disturbed tolerance to carbohydrates, chronic calculous cholecystitis, non-acute, varicose disease, reticular form, chronic atrophic gastroduodenitis, non-acute. Infectious hepatitis, sexually transmitted diseases, tuberculosis, allergic reactions are denied. No hemotransfusions. Bad habits are absent. Positive family history as far as hypertension goes (mother and father), nodular goiter. 2 pregnancies, 2 labors. The menstrual cycle is not disturbed.

Status praesens: height = 165 cm, weight = 86 kg, BMI = 31.6 kg/m^2. Upon referral, the general condition is relatively satisfactory. Hyperemic and edematous face. Skin with increased moisture. No skin eruptions. The peripheral lymph nodes are not enlarged.

Respiratory system: free nasal breathing, respiratory rate 16 beats per minute. Vesicular respiration, no rales.

Cardiovascular system: the cardiac area is not changed. Limits of relative dullness of the heart are expanded to the left, +2.0 cm outwards from the left midclavicular line. Clear and regular heart tones, no cardiac sounds, heart rate is 110 beats per minute, BP at examination is 150/100 mm Hg for the left hand, and 145/100 mm Hg for the right hand. Preserved pulsation on the peripheral vessels.

Digestive system: moist and clean tongue. Treated teeth. The abdomen is soft and painless upon palpation, involved in respiration. The liver and spleen are not enlarged. Constipation.

Urinary system: the renal area is not visually changed. Negative bilateral Pasternatsky's symptom. Free and painless urination. Involuntary flow of a large amount of light urine following hypertensive crisis.

Additional testing methods were used:

ECG as of December 15, 20 — sinus rhythm with heart rate of 102 beats per minute, diffuse changes in the myocardium, signs of decreased coronary blood flow in inferior and lateral sections.

Endocrinologist recommended to test total metanephrines and normetanephrines in daily amount of urine. Total — free and associated metanephrines and normetanephrines — intermediate products of adrenaline and noradrenaline metabolism. The test is used to diagnose and monitor adrenal tumors (pheochomocytoma) and nervous tissue (neuroblastoma, ganglioneuroma).

Unlike other products of catecholamine metabolism, antihypertensive drugs produce no effect on normetanephrines. However, for a proper analysis it is necessary to exclude serotonin-containing products such as bananas, chocolate, cheese, strong tea, coffee, alcohol. Physical exertion, stress, smoking, painful impact should be avoided three days prior to the suggested collection of urine for analysis. Regular drinking regimen is recommended during urine collection. Metanephrines are continuously produced in tumor cells and are not associated with release of catecholamine active fractions. Thus, urine metanephrine test is done irrespective of episodes of increased blood pressure. Intra-tumor process of catecholamine methylation occurs on a constant basis and does not depend on time when active catecholamines were released into the bloodstream. Determination of metanephrine and normetanephrine is a golden standard in diagnostics of pheochromocytoma. The method sensitivity is 99%. Specificity is 85–89%. Negative testing result is enough to exclude pheochromocytoma [6].

Metanephrine = 890 mg/day (less than 320.0), **nor-metanephrine** = 560 (less than 390) as of December 25, 20.

Creatinine as of December 25, 20 is 89.0 mcmol/l, ion selective analysis of electrolytes (**potassium** = 4.29 mmol/l, **ionized calcium** = 1.21 mmol/l, **sodium** = 133.0 mmol/l, chlorides = 102.3 mmol/l). Clinical blood analysis as of December 25, 20, **Hb** = 117 g/l, **WBC** = 11.75 *10^9/l, **PLT** 341*10^9/l, **RBC** = 4.09*10^{12}/l. Acid-alkali balance as of December 25, 20 **ABE**, mmol/l = 0.6, **GGLU** = 5.1, **cHCO3(P)** = 23.5, **cLac** = 0.7, **ctHBg\l** = 122, **mOsm, mmol\kg** = 270.2, **pCO2, mmHg** = 37.1, **ph** = 7.412, **pO2, mmHg** = 40.8, **sO2%** = 74.9, **time** = 16:32, **HCT** = 37.4.

Blood glucose = 7.5 mmol/l, **glycohemoglobin** = 6.0% (increased blood glucose is associated with pathophysiological effect of 'secondary' diabetes or disturbed tolerance to glucose due to intense glycogenolysis in the liver, decreased production of insulin due to stimulation of alpha-adrenoreceptors in the pancreas) [3].

Computed tomography of the abdominal organs with i/v bolus contrast enhancement as of December 28, 20. Conclusion: the testing was done in the multispiral regimen in accordance with the standard program with i/v bolus image enhancement. On a series of multispiral computed sectional images, the liver is of a regular shape, size, position with no foci of abnormal density and abnormal accumulation of contrast. Intrahepatic bile ducts and bile ducts are not enlarged. The gall bladder is not enlarged in size and contains no radiopaque stones. The pancreas is not located normally, has a multilobular

structure, the Wirsung's duct is not visualized. No focal changes and abnormal lesions are found in the glandular tissues. Parapancreatic cellular tissue is not changed. The spleen is not enlarged in size; it has regular outlines, and homogenous density with no focal changes. Kidneys are located as usual. Parenchyma has no foci of abnormal density. Renal collecting system is not enlarged. Renal vascular pedicles are structural. Paranephral cellular tissue is not changed. Adrenal glands are located as usual. The right adrenal gland is not changed. A round lesion with distinct and regular outlines sized 4.0*3.9*4.5 cm with +30 HU density is visualized in the left adrenal gland, in the body and medial limb.

Following administration of contrast, regular accumulation occurs: +88 HU during phase I, + 65 HU during phase II and + 50 HU in 10 minutes. The left renal vein goes along the inferior pole of the lesion. No free fluid is found in the abdominal cavity. The lymph nodes in the abdominal cavity and retroperitoneal space are not enlarged. No destructive bone changes are found in the scanning area. Conclusion: CT signs of abnormal lesion in the left adrenal gland.

Chest X-ray as of December 25, 20: on a survey radiograph, the lungs are expanded and have no focal and infiltrative changes. Pulmonary roots are not enlarged. The dome of the diaphragm is located normally. The shadow of the heart and vessels is not enlarged. Free sinuses.

The clinical diagnosis was made.

Principal diagnosis: pheochromocytoma of the left adrenal gland, mixed type (ICD-10: E27.5. Hyperfunction of the adrenal medulla).

Complications: Grade III symptomatic arterial hypertension. Symptomatic hyperglycemia.

Treatment: doxazosin has been given since December 28, 20 to conduct stabilizing preoperative preparation. Doxazosin is a selective prolonged α1-adrenoblocker for peroral use that produces an effect on the entire specter of α1-adrenoreceptors of resistance vessels. Half-life is 22 h. The effective dose is achieved in 2–3 h. The patient is given 4 mg doxazosin BID with up-titration to 20 mg once every 3 days with blood pressure control. In case of tachycardia, the patient was recommended to take bisoprolol in the initial dose of 2.5 mg OD in the morning under control of pulse. It was recommended to take bisoprolol after achievement of a stable α-blocking effect. In failure to comply with this condition, paradoxical worsening of hypertensive crises due to leveling of β2 dilatating effect of adrenaline is not excluded. The same was observed in the patient as a decreased severity of condition, duration and frequency of hypertensive crisis while taking antihypertensive agents recommended by a cardiologist prior to diagnosis.

No postural hypertension is found following intake of doxazosin and bisoprolol. Postural hypotension can develop during postoperative preparation using the abovementioned agents. Postural hypotension is considered by some doctors as a signal to withdrawal or decrease of a dose of α-blockers which is a typical mistake. In fact, occurrence of postural hypotension is associated with initial and pathogenetically explained deficiency of circulating fluid but not with the direct effect of the agents. Thus, upon occurrence of postural hypertension, the dose of α-blockers should not be reduced and drugs belonging to this groups should not be withdrawn [6]. The most severe patients include those with stable hypotension or tendency hereto between the attacks. In them, α-adrenoblockers belong to a means of choice, that allows to avoid the 'uncontrolled hemodynamics' and catecholamine shock [7]. Complete disappearance of hypertensive crises, BP stabilization and lack of tachycardia occurred in the patient by January 20, 21.

Based on ECG as of January 19, 21, the rhythm was sinus, with heart rate of 80 beats per minute and diffuse changes in the myocardium.

Acid-base balance (ABB) as of January 19, 21 **ABE**, mmol/l = 0.5, **GGLU** = 2.0, **cHCO3(P)** = 24.7, **cLac** = 0.6, **ctHBg\l** = 122, **mOsm, mmol\kg** = 267.1, **pCO2, mmHg** = 46.7, **ph** = 7.36, **pO2, mmHg** = 52.6, **sO2%** = 86, **time** = 6:10, **HCT** = 37,6, **potassium** = 3.1 mmol/l, ionized **calcium** = 1.18 mmol/l, **sodium** = 134.3 mmol/l, chlorides = **99.7** mmol/l). Clinical blood analysis as of January 19, 21 **Hb** = 122 g/l, **WBC** = 8.3 $*10^9$/l, **PLT** = $300*10^9$/l, **RBC** = $4.05*10^{12}$/l. Blood sugar = 6.8 mmol/l.

Criteria for surgical intervention in pheochromocytoma:

- decrease (disappearance) of hypertensive crises;
- stopping the hypovolemic syndrome (clinically and based on the results of preoperative measurement of the central venous pressure);
- avoiding rhythm disturbances;
- correction of metabolic disturbances.

Typical mistakes in preoperative practice:

- withdrawal or decrease of the dose of α-adrenergic blocking agents in postural hypotension and tachycardia during the initial period of medicinal agent intake;
- presence of initial hypotension is estimated as a contraindication to administration of α-adrenergic blocking agents;
- attempt to compensate hypovolemia and hypotension with fluid infusion or administration of pressor agents with no use of α-adrenergic blocking agents;
- attempt to compensate tachycardia with administration of β-adrenergic blocking agents with no previous use of α -blocking agents.

On January 20, 21, the patient had retroperitoneoscopic adrenalectomy on the left under combined anesthesia with ALV. Dermabond cyanoacrylate cement was applied. Postoperative period without abnormalities. Postoperative wound healed by primary intention. Results of a histological study (autopsy study of surgical specimen with tumor): pheochromocytoma of the left adrenal gland (4.5 cm in diameter) with focal vascular invasion and without signs of capsular invasion. The patient was recommended to limit physical load during 6–8 weeks after the conducted surgery with subsequent administration of Cortef (2 tablets in the morning, 1.5 tablets in the afternoon, 1 tablet at 8 p. m.). In a month, the dose of Cortef was gradually reduced with subsequent complete withdrawal of the medicine three months after prescription. When the dose of Cortef was gradually decreased, the patient had episodes of BP drop twice accompanied by a sharp general weakness, nausea, which slowed down the rate of lowering the dose of Cortef.

Since complete withdrawal of Cortef, the patient had an examination: since April 25, 21, ACTH was 28 pg/ml (10–185), urine cortisol test was 8.3 mcg/day (4.3–176), blood cortisol was 5.9 (3.7–19.4) mcg/dl. The patient underwent genetic testing for RET, VHL, SDHB, SDHD mutations.

Result of molecular and genetic testing as of July 09, 21 Target sequence analysis (Hereditary tumor syndromes panel) was performed. Examined genes: APC, ATM, ATR, BAP1, BARD1, BLM, BLPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDKN2A, CHEK2, EPCAM, FANCM, FH, FLCN, GNAS, GREM1, MAX, MEN1, MLH1, MRE11, MSH2, MSH3, MSH6, MUTYH, NBN, NF1, NF2, NTHL1, PALB2, PMS1, PMS2, POLD1, POLE, PRKAR1A, PTCH1, PTEN, RADSD, RADS1, RADS1C, RADS1D, RB1, RET, SDHA, SDHAF2, SDHB, SDHC, SDHD, SLX4, SMAD4, SMARCA4, SMARCB1, STK11, SUFU, TMEM127, TPS3, TSC1, TSC2, VHL, WRN. Conclusion: pathogenic/probably pathogenic gene variants associated with hereditary tumor syndromes are not detected.

DISCUSSION

According to retrospective and prospective genetic research done on large samples of patients with chromaffin tumors, almost 30% of patients have autosomal dominant genetic defects. In 32–38% of observations, mutations of genes associated with synthesis of succinate dehydrogenase, D-or B-subunit (SDHD or SDHB) are developed [5]. The disease occurs due to numerous functioning paragangliomas that have highly malignant potential. In these patients, phenotypic penetrance of pheochromocytome is 15–40%. Bilateral damage of adrenal glands is observed in 40% of cases, whereas extra-adrenal lesion is found in 70% [3]. In presence of this genetic defect, paragangliomas have mainly noradrenal type of secretion. Genetic testing was recommended as based on numerous genetic research on large samples of patients with chromaffin tumors it has been found out that 25–35% of patients with pheochromocytoma have genetic defects transmitted in an autosomal dominant type and responsible for the disease [7].

Thus, in 32–38% of observations, pheochromocytoma can occur in SDH syndrome or syndrome of functioning paraganglioma (SDH-B (1p35–36) or SDH-D (11q23) mutations along with A and C subunits). Pheochromocytoma is a sign of Von Hippel-Lindau disease (VHL-gene 3 chromosome mutation) in 30–35% of cases, type 2A multiple endocrine neoplasia or Sipple syndrome (mutation of the RET proto-oncogene of 10 chromosome in exon 10–16), type 2B multiple endocrine neoplasia or Gorlin syndrome (mutation of the RET proto-oncogene of 10 chromosome in codon 883 or 918 of exon 11) in 4–6% of cases, and 1 type neurofibromatosis or von Recklinghausen disease (mutation of NF-1 gene (17q11)) in 8–14% of cases [5].

One year following the surgery, the patient underwent follow-up examination and investigation.

January 20, 22. No complaints. Height =165 cm, weight = 92 kg, BMI = 34.07 kg/m^2.

Respiratory system: free nasal breathing, heart rate = 15 minutes per minutes, vesicular respiration, no rales.

Cardiovascular system: the cardiac area is not changed. The boundaries of the relative dullness of the heart are expanded to the left, +2.0 cm outwards from the left midclavicular line. Clear and rhythmic heart tones, no cardiac murmur, heart rate 80 beats per minute, BP upon examination 120/80 mm Hg (left hand), and 115/70 mm Hg (right hand). Peripheral pulsation is preserved.

ECG as of January 20, 22 –sinus rhythm with heart rate of 76 beats per minute, diffuse changes in the myocardium.

Metanephrine = 210 mg/day (less than 320.0), **nor-metanephrine** = 300 (less than 390) as of January 24, 22.

ACTH as of January 21, 22 ACTH = 38 pg/ml (10–185), urine cortisol test in a 24-hour sample of urine was 9.6 mcg/day (4.3–176), blood cortisol = 5.4 (3.7–19.4) mcg/dl.

MRI of kidneys and adrenal glands with contrast enhancement as of January 23, 22. Right kidney 95*45*43 mm, left kidney 96*48*45 mm. Clear and distinct outlines. Well-differentiated cortical and medullary substance. No changes in the vascular pedicles. No changes in the paranephral cellular tissue. Distinct and regular outlines of the right adrenal gland, the adrenal gland is of a regular triangular shape, sized 3.49*2.8 cm. The pedicular depth is 3.3 mm, homogenous structure of the adrenal gland. Condition following removal of pheochromocytoma of the left adrenal gland. No additional mass lesions are found in the removed adrenal bed. The lymph nodes are not enlarged. Free fluid in the abdomen is not visualized. Conclusion: condition following removal of the left adrenal gland due to pheochromocytoma in 2021. No MRI data of the recurrence.

CONCLUSION

A specific feature of the presented clinical case is that pheochromocytoma has not been diagnosed long-term. The patient diagnosed with hypertension has been examined by a cardiologist for a long period of time. It should be noted that the patient had a very high initial level of metanephrine and normetaneprine with a large tumor sized 4.0*3.9*4.5 cm and relative effectiveness of used medicines. It was difficult to take a decision under conditions of comorbid pathology bearing both endocrinological and surgical issues. Modern surgical correction that produced an indirect effect on prognosis and quality of life of the patient is important in this clinical case.

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SOCIOEXISTENTIAL, ETHICAL AND COMMUNICATION CONDITIONS FOR EMOTIONAL BURN-OUT AMONG MEDICAL WORKERS

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The burnout syndrome is a disease of modern societies. The acquired data prove that health professionals are more prone to the disease than others. Global programs supporting health professionals with this syndrome are lacking. In most severe cases, this can result in a loss of a professional. The purpose of this study was to detect socioexistential, ethical and communication conditions for emotional burnout among healthcare professionals to develop recommendations that prevent the examined syndrome. The authors consider a health worker as a significant and continuously renewable health resource (from Public Health perspective) and as a compassionate person without professional patterns of empathy. The basic study material includes data obtained during interviewing and questioning of medical workers at the Belarusian State Medical University and Belarusian Medical Academy of Postgraduate Education and content analysis of international interviews, medical chats and social networks. The principal methods include questioning, interviewing and content analysis.

Keywords: professional burnout syndrome, healthcare worker, continuously renewable resource, ethical knowledge, communication skills, sympathy, empathy

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СОЦИАЛЬНО-ЭКЗИСТЕНЦИАЛЬНЫЕ И ЭТИКО-КОММУНИКАТИВНЫЕ ПРЕДПОСЫЛКИ ЭМОЦИОНАЛЬНОГО ВЫГОРАНИЯ В СРЕДЕ МЕДИЦИНСКИХ РАБОТНИКОВ

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Синдром эмоционального выгорания является актуальной проблемой современного общества. Полученные данные позволяют утверждать, что представители медицинской профессии больше других подвержены данному заболеванию. Вместе с тем отсутствуют всеобщие программы поддержки медицинских работников, страдающих данным синдромом, что в особо тяжелых случаях может привести к потере медицинского работника. Цель исследования — выявить социально-экзистенциальные и этико-коммуникативные предпосылки эмоционального выгорания в среде медицинских работников для выработки рекомендаций, способствующих предотвращению изучаемого синдрома. Авторы рассматривают медицинского работника многоаспектно: как значимый и длительно возобновляемый ресурс здравоохранения с позиции Public Health и как сострадающую личность, у которой зачастую не сформированы профессиональные паттерны эмпатии. Основной материал исследования составляют данные интервьюирования и анкетирования медицинских работников, проводившиеся в Белорусском государственном медицинском университете, Белорусской государственной медицинской академии последипломного образования, а также контент-анализ международных опросов, медицинских чатов, социальных сетей. Основные методы: анкетирование, интервьюирование, контент-анализ.

Ключевые слова: синдром эмоционального выгорания, медицинский работник, длительно возобновляемый ресурс, этические знания, коммуникативные навыки, симпатия, эмпатия

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Occupational burnout (hereinafter known as burnout) is one of the most significant modern diseases that produces a significant effect on personal and public life and professional activity. The World Health Organization (WHO) officially included burnout into edition 11 of the International Disease Classification (IDC-11) as of January 1, 2022. In accordance with this decision, it is about a clinically significant syndrome, 'conceptualized as resulting from chronic workplace stress that has not been successfully managed' [1].

Based on the study of Dr. Torsten Heinemann, Professor of Sociology from Hamburg University, and Linda Heinemann, clinical psychologist and psychotherapist at the Goete University in Frankfurt, burnout is 'one of the most widely discussed mental health problems in today's society' [2].

In spite of numerous academic papers devoted to burnout, researches, training sessions and courses, burnout has not been overcome today and is becoming increasingly relevant. COVID-19 pandemic and related significantly restructured social and professional life contributed to this in many respects.

Burnout is especially relevant for some professions because the society places extremely high demands on them, communication with people here extends beyond functionalism, and professional activity is regulated using not only rigid legal but also soft ethical standards. Health professionals are definitely representatives of such professions.

Many modern studies [3] deal either with diagnostics of burnout or examination of burnout overcoming factors using social and mental tools (for instance, good organization management and teaching how to cope with stress). Without prejudice to the research and practices, authors believe that in the medical environment, the issues of burnout development are associated with, first, organizing the work of the healthcare system, second, need in competent training of medical personnel as far as professional knowledge and flexible creative clinical thinking, mental and emotional stability go, and, third, shortcoming of ethical and communication competencies of medical workers, inability to display empathy and respect towards a patient's autonomy.

Thus, the purpose of the study is to detect socioexistential and ethical and communication conditions for emotional burnout among healthcare professionals to develop recommendations that prevent the examined syndrome.

MATERIALS AND METHODS

The study was based on interviewing and questioning of doctors of the Belarusian State Medical University (BSMU), Belarusian Medical Academy of Postgraduate Education (BMAPE), communication with health professionals (doctors and nurses), patients and representatives of social organizations in the field of biomedicine. Content analysis of open access questioning of doctors about burnout, analysis of chats and social networks of healthcare professionals, discussion of cases and situations with doctors during thematic debates at the BMAPE were used as well.

STUDY RESULTS

The existing problem of burnout spreading among healthcare professionals should be considered in social and personal (existential) dimensions. This allows to outline ways of obtaining recommendations and practical measures that prevent development of burnout in medical environment.

In social dimension, researchers quote the following factors typical both of healthcare workers, and representatives of other professions such as manifestations of economic and sociopolitical instability, high competitiveness, improper labor conditions, non-observance of work and rest regulations, conflicts at work, absence of job guarantees, infringement of personal ambitions, doctor-patient communication problems and lack of satisfactory financial incentives [4]. They result in stress during a professional activity and, as a consequence, in burnout.

Objectively considering healthcare professionals as a significant resource of healthcare system (and the entire society), we can determine it as a 'renewable in the long term' because it takes six to fifteen (and more) years to prepare one specialist when the theoretical and practical educational components are combined. Moreover, a healthcare professional who works directly with patients should be fostered with ideas of humanism, mercy and empathy. It is difficult to do so using learning materials only. The healthcare professional should also develop communication, legal, research and other professional competencies.

We should not underestimate depletion of the resource renewable in the long term due to retraining of a healthcare professional, his switch to another professional field and possible labor migration in search for better working conditions, payment, emotional climate, etc.

Statistical data stating the exact percentage of healthcare professionals leaving the healthcare area because of emotional burnout are currently lacking. Their age, length of employment, rates, a number of patients examined per day are unknown (ranking the load related to outpatient attendance and home visits is required for doctors who work in a polyclinic). Thus, it is difficult to analyze how many healthcare professionals and of what specialties suffer from burnout to the greatest extent, how their number changed during the COVID-19 pandemic, etc. An extensive scientific and practical examination of burnout among healthcare professionals is required in the post-Soviet area during COVID-19 pandemic taking into account labor conditions, set objectives and possibilities of their implementation. The research is needed to develop relevant recommendations to prevent burnout among healthcare professionals, as it will improve social conditions, structure labor of healthcare professionals and develop the system of healthcare organization.

In the social dimension, we consider prevention of burnout among healthcare professionals in the context of functioning and improvement of Public Health, system organizing medical activity and system of society-based medical education. In the personal (existential) dimension, it's necessary to focus mainly on psychological and emotional factors that lead to burnout of healthcare professionals and possible ways of their prevention.

As far as the existential dimension goes, considering a healthcare professional as a separate person, but not as the 'resumed in the long term' healthcare resource, signs of emotional burnout are manifested in the broadest sense — from personal crisis to suicide. For instance, according to US-based researches, 300–400 therapists die because of burnout (the data are approximate with no exact statistics left). The thoughts emerge in up to 7% of healthcare professionals who participated in the interrogation, whereas 35% noted that they wouldn't ask for help in case of those thoughts [5].

According to WHO, healthcare professionals commit suicide 1.5–4 times more frequently than representatives of other professions, irrespective of gender. This is most frequently observed among those who have access to medicinal preparations used as a tool for suicide [6, 4].

Among possible preconditions leading to such a tragic scenario, the lack of ethical and communication knowledge and skills is of great importance. Ethical pluralism, collision of absolutist and utilitarian strategies, replacement of an ethical constituent with common sense, collision of ethical ideology and legal standards, political collisions, and economical factors become a heavy load for a modern healthcare professional.

The issue is that ethical (bioethical) preparation of healthcare professionals frequently remains at the level of the Hippocratic oath. It doesn't include examination of modern developments, recommendations, provisions of international instruments and, finally, principles and rules of modern bioethical ethics and cases extracted from Russian and international medical practice. Holding discussions regarding biochemical (medical) ethics, authors repeatedly faced the issues of total ignorance by doctors (nurses) of the BMA International Code of Medical Ethics [7], Convention on Human Rights and Biomedicine [8], etc., basic ethical recommendations, for instance, on working with children, patients with mental diseases, taking medical decisions regarding the end of life, algorithm of working with informed consent, ethical and legal issues of compliance with medical confidentiality, etc. [9].

Fostering modern ethical consciousness, ability to navigate in complex and multiple-valued situations and understanding significance of the multidisciplinary approach

Table. Table of mutual expectations

Position No.	Patient	Physician
1	'Empathy', 'kindness', 'affection', 'dialogue'	'Friendly', 'positive-minded', 'sociable'
2	'Being respectful' and 'attentive' to patients	'Respect', 'trust in a doctor'
3	'Intelligence and knowledge', 'love for profession'	'Honest', 'calm and tidy'
4	'Commitment', 'patience', 'delicacy', 'intuition', 'seriousness', 'sense of humor'	'Briefly and clearly described symptoms', 'strict adherence to doctor's prescriptions'

in healthcare professionals constitute an obligatory condition for professional medical education, including the system of advanced training among healthcare professionals. Thus, advanced training courses such as Ethical and legal activity framework of healthcare ethics committees and commissions, Ethical and legal competence of a doctor, Bioethical aspects of communication in healthcare, created to develop ethical skills among doctors based on modern ethical and legal principles and rules are very popular at the Belarusian Medical Academy of Postgraduate Education. A serious disadvantage is that the capacity of these courses is currently insignificant. That's why they are basically visited by healthcare supervisors who are supposed to educate their employees later. It would be correct to expand the education/provide advance training to ordinary doctors and nurses using ethical (bioethical) subjects in medical universities, constant training, courses, master classes.

The activity can be carried out not by state structures only, but also by public medical associations and organizations, journals, etc. A positive example can be represented by a number of conferences in Minsk in 2016–2019 organized by the Ministry of Health of the Republic of Belarus supported by the Committee on Bioethics (DH-BIO) at the Council of Europe, on Human Rights and Biomedicine for Medical and Legal Employees; Scientific and Practical Conference 'Ethical and Legal Issues of Ensuring Rights of Patients and Healthcare Professionals under conditions of modern healthcare' (Jurspectr) held in 2019, constant ethics column in Head Nurse journal (Grevtsov Information Agency), organization of 'Doctor-patient' column on site of Center for Republican Bioethics (https://bioethics.belmapo.by/), etc.

Another significant factor that indirectly influences occupational burnout in the medical environment includes expanded patient's autonomy. On the one hand, this is a regular process that develops self-consciousness of a modern patient; on the other hand, the process also has a negative constituent resulting in a growing number of cases of the so-called 'patient's extremism' via unreasonable complaints about doctors and nurses. According to the interview held in November 2019 by Doctor at Work social network and RNC Pharma, 63% of patients asking for help display inadequate behavior, 32% of doctors have come across rudeness of patients and consider this as a typical behavior, and only 3% of them noted that during a medical interview, patients act in a polite and civil way [10].

At the same time, the growing autonomy of a patient should be taken both as a natural process of human and society development, and as the developing process of 'separation of responsibility', which recognizes the absolute right of a patient to take decisions about his own life and health. Unfortunately, healthcare professionals frequently refuse the right of a patient for the autonomy, assuming that they are better aware of the situation and can take a better and more informed decision [11]. On the one hand, a healthcare professional puts pressure with subsequent additional emotional burden, and, on the other hand, he/she is not ready (and is not always able) to listen to a patient. This prevents him/her from sharing responsibility and letting go of the situation.

As far as burnout prevention goes, special attention is given to the skill of empathy. In the medical environment, it is taken as a feeling that comes with experience. However, a healthcare professional needs to be taught a correct manifestation of empathy, as this developed skill is an burnout barrier. Empathy of a healthcare professional should not be taken as regular compassion, but is more like sympathy with involvement into the problems of others, joint compassion with emphasis on emotionality and own involvement into the problem [12]. Empathy, which is essential to a healthcare professional without an effect of burnout intensifying factor, means practical compassion and involvement, with emphasis on sympathy through activity, practical aid and using practical skills for its implementation.

During an anonymous interview of healthcare professionals and patients (50 medical practitioners and 50 patients) held in 2018, those surveyed were offered to enumerate and distribute by significance/positions (1–4) attributes determined by them as essential to doctors/patients and expected to be seen during attendance. While developing a table of mutual expectations, almost every patient placed empathy and communication skills first, and respect second. The same goes with priorities of healthcare professionals towards patients: first, positive mood and ability to communicate, second, respect. Moreover, emphasis on professional data in the list of patients' expectations was made in the third line of the summary table only denoted as 'intelligence and knowledge' and 'love for profession' (table).

Thus, social skills should be obligatorily developed in every healthcare professional. They include not only knowledge and proper ethical values, but also an ability to use communication skills and technologies of communication. This can be promoted using special training courses, seminars, further education courses (for instance, such courses as 'Culture of social relations' or 'Technologies of business communications' developed at the department of public health and healthcare of the Belarusian Medical Academy of Postgraduate Education).

Basic ethical and communication principles and practical skills that promote positive doctor-patient relations and, as a consequence, prevent a healthcare professional from emotional burnout, include as follows:

- being patient-centered and human-centered;
- display respect for a patient comprehended as respect for a patient's dignity, his values, priorities and decisions, including when the patient consciously refuses help (a healthcare professional can explain and give an advice but has no moral right to put pressure, urge and teach);
- follow the rule of telling patients the truth (about the diagnosis, condition, perspectives, etc.): the truth should be told but this can be done gently and carefully taking into account circumstances and condition of the patient;
- respect confidentiality of patients' data: remember that conversation regarding the diagnosis, treatment, prognosis and any other personal information should

be held with the patient or his/her legal representatives (if the patient is not able take decisions) or with the persons mentioned by the patient;
- an ability to listen to and hear a patient, an ability to start and end a dialogue, prohibition to use euphemisms, uncontrolled vocabulary, slang, etc.;
- encouraging a patient's communication with his close relatives as this can be the best medicine and the most successful therapy for the patient;
- requirement not to use urgency/occupation as a reason for disrespect or exclusion of formalities when communicating with patients (for instance, not to say hello or knock on the door of the ward, etc.);
- preserve and respect corporate culture, in particular, never display a negative attitude towards actions of other healthcare professionals;
- trying to take care of self by establishing communication borders with a patient (relatives) and communication time limits, having an ability to switch between other (including personal) problems and issues [13].

CONCLUSIONS

Considering highlighting of burnout in modern scientific literature, interviewing and interrogating doctors, patients and nurses and doctors, the authors made certain conclusions.

First, to prevent burnout among healthcare professionals, healthcare system requires restructuring and humanization based on the principles of human centricity, patient-centered practice, and specifics of continuously renewed resource of healthcare professionals. Medical professionals need to be trained in 'self-saving'; monitoring of the current burnout-related situation, management of psychological counselling, building a single system of psychological support and rehabilitation of healthcare professionals affected by the crisis are required. In our opinion, the work should be based on significant country studies that enable to detect an exact percentage of healthcare workers suffering from burnout. Second, ethics and communication training programs that prevent and restrain the process of emotional burnout among healthcare professionals need to be expanded within restructuring of healthcare system. The programs should be held on a constant basis as continuing education courses, thematic conferences, public initiatives, training courses, seminars, etc.

Third, resting on the time inquiry to develop the patient's autonomous model, it is necessary to work more with people regarding the issue of medical literacy, respect for medical profession, ethical and communication standards of behavior, on the one hand, and improve the system of legal standards that protect a healthcare professional not just from unjust 'patient's extremism', but also from any illegal behavior towards medical personnel, on the other hand.

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THE MODELS OF MEDICAL EDUCATION: HISTORICAL ASPECTS, CURRENT CONDITION AND CONCERNS

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The article describes stages of medical education development in the chronological order and discusses the principal models of university organization and the process of evolution of scientific approaches to their formation throughout history. Preconditions for reviewing approaches to a subsequent change in the model of university education and direction of the search at the core of the modern educational concept are enumerated. Advantages and shortcomings of third-generation universities formed under the effect of the industrial revolution are separately discussed. The value and role of the university at the modern stage of society and economy development are being considered. It is concluded that educational needs require fundamental transformation, selection of the widest specter and most qualitative level, implemented scientific and educational programs, search for new approaches to mass and elite education. State support, protection, commercialization of knowledge, interdisciplinary integration and cooperation with the leading companies and research structures as part of national scientific laboratories will enable transfer of technologies to develop a new generation university that corresponds to modern tasks and needs of the country intensive development.

Keywords: educational models, university transformation, research university, third generation university, research skills, interdisciplinary approach

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МОДЕЛИ МЕДИЦИНСКОГО ОБРАЗОВАНИЯ: ИСТОРИЧЕСКИЕ АСПЕКТЫ, СОВРЕМЕННОЕ СОСТОЯНИЕ, ПРОБЛЕМЫ

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В статье в хронологической последовательности описаны этапы развития медицинского образования и обсуждены основные модели организации университетов, а также процесс эволюции научных подходов к их формированию на протяжении истории. Перечислены предпосылки пересмотра подходов к последовательному изменению модели университетского образования и направления поиска, положенные в основу современной концепции образования. Отдельно рассмотрены преимущества и недостатки университетов «третьего поколения», сформировавшихся под влиянием промышленной революции. Обсуждаются значение и роль университета на современном этапе развития общества и экономики. В заключение делается вывод о том, что потребности в сфере образования требуют от университетов кардинальной трансформации, выбора максимально широкого спектра и качественного уровня, реализуемых научных и образовательных программ, поиска новых подходов в рамках массового и элитарного образования. Государственная поддержка, протекционизм, коммерциализация знаний, междисциплинарная интеграция и сотрудничество с ведущими компаниями и научно-исследовательскими структурами в рамках национальных научных лабораторий позволят обеспечить трансфер технологий для развития университета нового поколения, отвечающего современным задачам и потребностям интенсивного развития государства.

Ключевые слова: образовательные модели, трансформация университета, научно-исследовательский университет, университет «третьего поколения», навыки научной работы, междисциплинарный подход

Вклад авторов: Ч. С. Павлов разработал концепцию и структуру статьи, подготовил выводы и доработал текст статьи; В. И. Ковалевская внесла существенный вклад в концепцию статьи, изучила литературные источники, провела анализ данных, подготовила текст статьи. Т. М. Литвинова, Б. А. Волель осуществляли научное руководство, разработали концепцию статьи, доработали текст, окончательно утвердили публикуемую версию статьи. Все авторы утвердили окончательную версию статьи.

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New scientific ideas and discoveries alter the world and humanity, set up an alternative view of the surrounding reality. Rapid development of technologies of the fourth industrial revolution (4IR) and digital transformation affect every aspect of human life: health, professional activity, principles of social interaction, meaning and values of a human life and activity, ecological limitations [1–4]. In many countries, higher education reforms change the vector of university development turning it into the new center of knowledge generation and factor of economic growth [4–6]. The achievement of educational theory in the 20th century consisted in understanding that education is a part of social process and that it determines the trends of the

country development [7]. A global change in the educational model of higher medical schools directed at strengthening the share of a scientific component determined the need to combine evidence-based medicine and research activity to achieve the new quality of medical education [8].

HISTORY OF FORMATION AND BASIC MODELS OF UNIVERSITIES

The first European Universities such as the University of Bologna (1158), University of Paris (1180), University of Oxford (1188) and University of Cambridge (1209) were founded and existed under the patronage of the church. They embraced three schools (theological, medical and legal). The medieval science was based on scholasticism, ability to speculate and conduct a debate, the education was of dogmatic nature and required memorization. The basic ideas most essential to the Renaissance were those of the European humanism, when human beings, their freedoms and values were placed at the center of meaningful life. In the 16th century, the universities were separated from the church following the Renaissance ideas. During that time the methods of teaching were developed in a different way, widening the scope for development of the research thought. The University of Padua was able to maintain independence from the influence of the church. Andreas Vesalius, who was a doctor and anatomist at this University, dissected the bodies of executed criminals during his lectures to gain better knowledge of anatomy and understand how a human body is functioning. Students of the University of Padua were allowed to discuss what they saw during autopsy at the anatomical theater, have doubts and disputes with teachers and express objections to Galen's works. The scientific method of observation and discovery in the Art of Perspective and Drawing of Volume was used to create the first Handbook of Anatomical Charts with the images of a dissected body (1543). The emergence of book printing was accompanied by appearance of scientific journals to distribute research findings in the professional community.

In the 17th century, sciences associated with examination and description of nature are coming to the foreground. Willian Harvey had a series of experiments, the results of which were opposed to the known theoretical assumptions of those times, and created the basis for experimental medicine. Discovery of the circulation and description of how the heart works were published in Demotu tractate (On movement of the heart and blood). Owing to Francis Bacon, Robert Boyle and Isaac Newton, an experimental approach in the 17th century became the basis of scientific work that added to theoretical reasoning; the foundations of research thinking and basis of the scientific approach to the world were laid stating that classical physics is a deterministic science that can explain everything, and if something is unclear, then there is no knowledge of the issue. The dominant content of science included chains of reasons and consequences describing mass and energy, the fundamental theory of mechanistic understanding of the world and math of Newton, which is of quantitative nature, provided for very exact calculation of various amounts and attached special importance to thinking in exact sciences. Physics was developed launching medical discoveries. Giovanni Borelli used achievements of mechanics and physics to study the musculoskeletal system, laid the foundation of biomechanics, and developed the idea of 'structure of a human being as a complex mechanism'. Achievements of adjacent sciences allowed the scientists of those times to make such discoveries as determination of lung volume and strength of contraction of the cardiac muscle.

By the 18th century, the European science has already had the basis of an academician tradition: scientific methods that appeared out of systematic experiments and skills of scientific argumentation originating from the medieval scholasticism. These were skills of separate scientists interested in knowledge and discovery distribution and sharing. During the era of the great geographical discoveries and colonial conquests, collection of artefacts and actual data in various areas required description, systematization and analysis of obtained colonial collections and provided experience of writing and publication of scientific texts at the universities. By the 18th century every university had already issued its own journal.

The first model of a classical university was established in Prussia in the 19th century, when the country turned into a center of research innovations and attracted people from Europe and Russia being a place where they could complete their education. The new university concept was based on the Enlightenment ideas associated with development of rational and free thinking [9]. Minister of education of Prussia Wilhelm von Humboldt, a diplomat, philosopher and linguist, followed industrial and technological ambitions of Frederick William, king of Prussia, and convinced him to conduct an educational reform and establish a new university in Berlin (1810) with independent work but not pure memorizing being at the core. It was for the first time when studying and research came together at the University: a teacher was a student's academic advisor, a student had to conduct independent research, and not just learn lectures by heart. Friedrich Schleiermacher who was one of the first professors and ideologists of the Berlin University claimed that an important role of a university was to teach students to obtain new knowledge independently and stimulate their interest in scientific research.

University innovations applied during organization of the scientific process resulted in emergence of new research laboratories. They attracted leading scientists from different countries. Now not solo geniuses, but groups of scientists who conducted joint experiments and discussed the results worked on this research: the studies became organized and systemic. Research studies were based on the rational method used during experiments and ability to argue and prove their point of view, they were open for inspection and verification of the results by other researchers, and had to be published in special journals and books. The Humboldtian universities obeyed the rules of pure science development. In the 19th century, a sum of factors in the form of financial investment into the national modernization of Prussian industry, emergence of new forms of scientific work (laboratories), invention of new industrial technologies which promoted science development (for instance, first synthetic colorants that could be used to color the cell and see its structure clearly), enabled to shape the currently existing principles of fundamental research organization. Universities in different countries that followed the Humboldtian model acquired the status of national universities and became a matter of pride, especially since establishment of the Nobel Prize (1901). Even now the prize goes to the countries where the leading universities are located.

Thus, at the end of the 19th century, a model of traditional classical research university was formed in Europe and Russia; the idea of 'nourishing a spirit of a reality study in a student' proven its effectiveness in science development and its interconnection with education at universities [10].

As part of the traditional classical German university, a student needs to have the most common and universal thinking abilities, master the methodology of scientific research and reasoning. This will be the tool used to acquire the knowledge a teacher can't foresee [10]. Sergey Gessen who was one of

the leading Russian and internationally recognized researchers of education wrote that the sign of the higher scientific school and essential part of teaching included demonstration of the research process to students. Thus, in his opinion, a teacher should be an active scholar, and a student should be a participant of the teacher's research. With a lecture, a teacher aims not to report the research results, but to outline a process (how the scientists came to these outcomes to make students independently check the data and conclusions; at seminars, a teacher acts as a critic of the study conducted by the student) [10].

Academic universities of Europe based on pure science with their scientists forming a distinctive caste drew the line fundamentally and intentionally and casted anathemas on any commercialization or attempts to make scientific discoveries popular. The classical example is the Cambridge University that gave the world the largest number of Nobel laureates and where theories of Newton and Darwin were disclosed, Rutherford split the atom, James Watson and Francis Crick determined the double-helix structure of DNA. The Cambridge University strongly resisted any attempts of applied use of scientific knowledge at the University till the middle of the 20th century [6, 11, 12].

The second university model began its formation in the end of the 19th century and was the embodiment of ideas of John Dewey, an American philosopher and educator [9]. This model differs from the classical one, because science and education are intended for practical implementation and solving tasks. During the educational process, students have to master practice-oriented skills. From the very beginning, a student has to participate in applied research and transformation programs that require development of industries of the country [13]. Dewey's concept is based on pragmatism ideology: development of scientific critical thinking (study of dilemmas, formation of hypothesis and awareness of decision consequences) and practice-orientation (showing how to solve life problems) [14]. Continuing Dewey's ideas, William Kilpatrick offered to stimulate accomplishment of practical tasks in social environment; he was the first to introduce the method of projects in the educational process [15].

During the second half of the 20th century, after the World War II, funding of science and education was sharply increased leading to the mass explosive growth of higher education, including the USA, in the background of economic and infrastructure recovery. Incentives of additional financing of higher education were space exploration and cold war.

According to Noam Chomsky, before the second World War the USA were a kind of a cultural and intellectual province; scientists from the USA were sent to Europe to study culture and science [16]. During the war, a vast majority of academic staff fled from Europe to escape the Nazis, which had a major influence on universities and higher education. Transfer of scientific methodology and technologies, substantial amounts spent on science by the US Government resulted in formation of high-tech economy within 10 years (computers, microelectronics, satellites [16].

An aggregate of social and cultural processes in the 1960–1970s promoted social debates associated with the educational reform. The issues of equality of a human activity and world ecosystem have come to the forefront. Education and researches in the western countries and in Russia are now associated with fundamental tasks of human personality formation and development, and not just with preparation for professional activity [17–20].

Gregory Bateson, graduate at Cambridge, visiting professor of Harvard, professor of Columbia University and University of California (USA), was among the first scientists who initiated discussion of the systemic approach to the world and human beings. He was a founder of the systemic and holistic approach in interdisciplinary studies of natural and social sciences: synthesis of cybernetics and anthropology, biological evolution and genetics, key researches in psychiatry. His holistic view of the world contained a complex network of relations with a human being a part of it. He believed that facts could be interpreted and research-based processes could be comprehended only if the systemic worldview is available. The source of concerns and the way how they are resolved (human thinking: it is necessary to see and think in a new way) have an integral and ethical responsibility towards the world and self. Bateson introduces the term 'mind ecology'. It is a way when a research thought is developed as combined with the rational and integral vision of the examined phenomena when the pervading unity of processes, the same laws are inherent to different areas (for instance, psychiatry and quantum physics) [21].

'The nature of the study does not let the researcher know what is being examined by him until it has been examined; there is no guide in his pocket to tell him which points have to be crossed, as only the experience of those who walked through this path is available. Deep layers of the mind lead a scientist or a painter to the feelings and thoughts related to the problems that are his problems somehow. The guidance seems to act long before a scientist obtains any conscious knowledge of the purposes. But we don't know how this happens' [21].

Awareness of the need in the interdisciplinary and integral approach to the studies influenced the occurrence of research centers outside the universities. Soon after the World War II, research organizations (European Organization for Nuclear Research) were founded based on physical research. They demonstrated effectiveness of researches as part of the interdisciplinary approach, when a team of highly qualified specialists participate in the study [6]. Experience of scientists previously working in a large multidisciplinary team of Oak Ridge National Laboratory (Manhattan Project) was essential to DNA recovery. Maurice Wilkins, a biophysicist, who came to the Royal College to study chromosomes, took the task as a physicist and applied the knowledge of the structure of an atom in practice with the help of new technologies. He assumed that DNA functioning and reproduction can be deciphered if its structure is understood. Wilkins was supported by Rosalind Franklin, a biophysicist and radiologist, who took X-rays and recorded various DNA samples. Her photograph 51 made it possible for James Watson and Francis Crick in Cambridge to discover the double-helix structure of DNA. Transfer of experience, synthesis of methodology from other areas using the integral approach promoted their discovery. For now, the majority of scientists admitted that interdisciplinarity should become the quality of the modern university, a site where competing ideas and discussions intersect.

THE MODERN MODEL OF UNIVERSITY EDUCATION

We witness gradual global awareness of shifted paradigm in science and education. Just like other areas of human activity, education is associated with social and political society-based processes, fundamental scientific paradigms and conceptual frameworks of the worldview [22].

Discoveries of quantum physics in the beginning of the 20th century produced a huge impact on human ideas of the entire world and ways to interact in it, as well as scientific approaches used in natural and humanitarian experimental trials. The classical approach describes phenomena as they

are irrespective of the utilized methods of trials. As part of quantum concept, the researchers should take into account that the observation result is fundamentally dependent on the device being used. The classical system measurement can fail producing an effect on the system condition; this is not the case with the quantum system. Development of quantum physics enabled understanding the fundamental value of probability not associated with the lack of knowledge. The phenomena were described as an aggregate of interdependent conditions. Richard Feynman, a famous physicist, displayed a condition of superposition or quantum state in his experiment, the essence of which lies in the mutual interference. Thus, when an electron is being observed and when its condition is being captured, the electron acts as a common particle; when an observer doesn't look at it, the electron exerts wave properties, meaning, that it 'acts' and behaves in accordance with the observer's actions. The observation frees an object from a set of uncertain quantum conditions and shifts it into a manifested and observed condition [23]. The discoveries influenced all the areas of the scientific life. For instance, in scientific articles it was normal to mention the used system and resources of searching for scientific information, description of the used methods as factors that determine the risk of errors when estimating the research results by other researchers.

New technologies responsible for unforeseen changes in the world raised concerns about the inevitable transformation of universities as part of the 4IR. Prof. Ronald Burnett from the University College London Institute of Education was the first who mentioned the concerns in his inauguration speech in 1997. Today, his ideas serve as the social and philosophical basis for transformation at universities. According to Burnett, we live in a supercomplex world, and all our theories and structures are checked and challenged on a constant basis. That's why we need new ways of life in such a fragile and supercomplex world with variability and uncertainty of structures and systems in its basis. New methods of education should be inevitably developed. They would 'teach to formulate doubts and obtain an experience of understanding disputability as it is'. The lectures should be replaced with interactive methods of education that enable students to work with contradicting ideas and perspectives. Different forms of debates and seminars are designed to teach student how to participate in discussions and debates that were very respected by the medieval universities. Participating in giving birth to supercomplex things, the university has to show how to live with them [24, 25].

Development of the university research vector is the principle aim of higher education reform for today. Research studies require significant financial contributions. That's why universities had to solve pragmatic tasks, providing for a high-tech component of economy growth. Facing universal cuts in public financing since the 1990s in Western countries, in particular, universities had to search for additional financing sources, including commercialization of studies and deriving benefit from know-how. In Europe — but not in the USA — classical universities admitted the situation quite recently and in a reluctant way. In the 1960s only the Cambridge was slowly surrounded by consulting companies (*Cambridge Consultants* etc.) founded by the graduates 'to make the brains of the Cambridge University solve the tasks of the British industry' [6, 26]. In 1997, Gordon Brown who became Minister of Finance of the Great Britain, reported to the Government that knowledge economy depends on the possibility to turn research results into commercially successful products. His report officially recorded 'the transfer of technologies for public purposes' as a vector of development of universities along with scientific research and education [6].

The true purpose of the universities was to encourage thinking, conduct independent and creative research, question the established truths, and open new horizons without sticking to external constraints. It is important not to cause irreparable harm to the society by turning universities into the institutions aimed to commercialize science and manufacture products for the market [16]. There is inevitably a question whether a society with full contribution of education into economic reproduction or a society that creates conditions for development of every human being can be called a developed society [25]. Classical universities faced an internal dilemma: ideal scientific impulses to search for truth and meaning, on the one hand, and pragmatic need to develop knowledge for economic growth, on the other hand [25, 27]. Scientists are attracted by thinking about the meaning of life and structure of the world, a possibility to look over the edge and reveal something new about the world, but not by the future profit [27].

In medicine, new knowledge is rapidly implemented into the real practice: robotization and artificial intelligence, bio- and nanotechnologies, augmented reality and neurotechnology become the possibilities of development if they are based on the responsibility and value of serving the humanity [24, 28]. New technologies cause fear and anxiety, they try to replace the human role for the first time, and humanity hasn't faced such threats yet. Though artificial intelligence is just a combination of algorithms used to train a machine, it is progressing very rapidly and threats are so unpredictable that understanding the human place, role and possibilities is taken as forms of survival; that is why almost all discussions regarding higher education concern concepts of individual development and self-realization of a human being [29, 30].

The ethical issues such as role of science and universities in the development of a human being and society of the future are resolved using the ecological model of a university that promotes interrelation of different ecosystems: natural, social, personal, economical, educational and cultural, as they create a set of values and limitations for a university science and system of education in the 4IR era [25, 31].

The complex approach that considers all factors is basic in the development of modern education. Key features of the modern research university that follows the requirements include high level of teaching and science, modern material resources and infrastructure for research (libraries, laboratories, clinical centers), cooperation with state and commercial structures, relations with industry, collaboration with other universities [32, 33]. The universities are commonly funded at the national level and with additional private sources [32].

The university model that combines science and education is generally accepted by the modern knowledge economy. It is a mixed type of a research university with traditions of fundamental studies of a classical university which is aimed to solve applied tasks [4, 6, 32, 33]. This model forms the basis of the most effective universities such as Harvard and Stanford universities, Massachusetts Institute of Technology in the USA, Cambridge University in Europe, Zhejiang University in China and University of Technology and Design in Singapore [34, 35].

According to Prof. Johan Wissema from the Technical University Delft who suggested the concept of third generation universities, it's important for a university to develop in the vector of 'open innovations' and interact with companies and other research structures: it should become a web-based international 'know-how hub' with a developed infrastructure and different development sources within the same site. The fundamental and applied trials conducted at the third-generation universities are related not through education and research only, but also through

know-how commercialization and scaling, collaborations with high-tech companies, cooperation with high-status universities through research projects, management of interdisciplinary studies at the institutes which are part of universities [6].

CONCLUSION

Educational needs require that universities should undergo qualitative transformation, select the widest possible spectrum, most qualitative level, and implemented scientific and educational programs, and search for new approaches as part of mass and elite education. State support, protection, commercialization of knowledge, interdisciplinary integration and cooperation with the leading companies and research structures as part of national scientific laboratories will enable transfer of technologies to develop a new generation university that corresponds to modern tasks and needs of the country intensive development.

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