Scientific and Educational Eastern European Medical Cluster

MEDICAL ETHICS

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

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

Indexed in RSCI

Open access to archive

Issue DOI: 10.24075/medet.2023-04
The mass media registration certificate серия ПИ № ФС77-81021 от 02 июня 2021 г.
Founders: Yaroslavl State Medical University (Yaroslavl, Russia)
Pirogov Russian National Research Medical University (Moscow, Russia).
Publisher: Pirogov Russian National Research Medical University; adress: Ostrovityanov Street 1, Moscow, 117997, Russia

Approved for print 08.10.2023
Circulation: 100 copies. Printed by Print.Formula
www.print-formula.ru

Научно-образовательный медицинский кластер Восточно-Европейский

МЕДИЦИНСКАЯ ЭТИКА

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

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

Журнал включен в РИНЦ

Здесь находится открытый архив журнала

DOI выпуска: 10.24075/medet.2023-04
Свидетельство о регистрации средства массовой информации серия ПИ № ФС77-81021 от 02 июня 2021 г.
Учредители: ФГБОУ ВО «Ярославский государственный медицинский университет» Минздрава России (Ярославль, Россия);
ФГАОУ ВО «Российский национальный исследовательский медицинский университет имени Н.И. Пирогова» Минздрава России (Москва, Россия).
Издатель: ФГАОУ ВО «Российский национальный исследовательский медицинский университет имени Н.И. Пирогова» Минздрава России;
адрес: ул. Островитянова, д.1, г. Москва, 117997, Россия, 8(495)434-03-29

Подписано в печать 08.10.2023
Тираж 100 экз. Отпечатано в типографии Print.Formula
www.print-formula.ru

MEDICAL ETHICS **4, 2023**
МЕДИЦИНСКАЯ ЭТИКА

Contents
Содержание

EDUCATION, HEALTH, AND MERCY. TRAINING SISTERS OF MERCY AT THE YAROSLAVL MEDICAL UNIVERSITY

Khokhlov AL[1], Zhbannikov PS[1], Zarov AYu[2], Firsov DE[1] ✉, Hieromonk Agafangel (Shkurankov AV)[3], Makarov SV[1]

[1] Yaroslavl State Medical University, Yaroslavl, Russia

[2] Central Clinical Hospital of St. Alexy Metropolitan of Moscow of the Moscow Patriarchate of the Russian Orthodox Church, Russia

[3] Department for Charity, Social Service and Relations with Medical Institutions of Yaroslavl Diocese, Russian Orthodox Church, Russia

In the modern world, traditions of social work are highly demanded both by the professional medical corporation and entire society. The experience of hospital volunteering is particularly relevant in relation to palliative patients. Volunteers involved in practical healthcare should have the corresponding level of qualification. The issue is solved by training and retraining of hospital volunteers and specialists of various levels at medical educational institutions. Junior medical nurses (sisters of mercy) have been trained at the Yaroslavl State Medical University since 2023. The specialized department of palliative medicine on the basis of Clinical Central Hospital of St. Alexy Metropolitan of Moscow of the Moscow Patriarchate of the Russian Orthodox Church was created at the Yaroslavl State Medical University. It is the interaction with state, social and confessional structures that allows to solve issues of practical implementation of the skills obtained by volunteers considering a wide range of community demands.

Keywords: hospital volunteering, social initiative, 'sisters of mercy', Yaroslavl State Medical University

Author contribution: Khokhlov AL, Zhbannikov PS, Zarov AYu, Firsov DE, Shkurankov AV, Makarov SV — collection of statistical data, preparation of text.

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

Received: 06.10.2023 **Accepted:** 15.11.2023 **Published online:** 29.12.2023

DOI: 10.24075/medet.2023.027

ОБРАЗОВАНИЕ, ЗДОРОВЬЕ, МИЛОСЕРДИЕ. ПОДГОТОВКА СЕСТЕР МИЛОСЕРДИЯ В ЯРОСЛАВСКОМ МЕДИЦИНСКОМ УНИВЕРСИТЕТЕ

А. Л. Хохлов[1], П. С. Жбанников[1], А. Ю. Заров[2], Д. Е. Фирсов[1] ✉, Иеромонах Агафангел (А. В. Шкуранков)[3], С. В. Макаров[1]

[1] Ярославский государственный медицинский университет, Ярославль, Россия

[2] Автономная некоммерческая организация Центральная клиническая больница Святителя Алексия Митрополита Московского Московской Патриархии Русской Православной Церкви, Москва, Россия

[3] Отдел по благотворительности, социальному служению и взаимодействию с медицинскими учреждениями Ярославской епархии Русской Православной Церкви, Ярославль, Россия

Традиции социального служения в современном мире востребованы как на уровне профессиональной медицинской корпорации, так и общества в целом. Особенно актуален опыт больничного добровольчества в отношении пациентов паллиативного статуса. Привлечение волонтеров в практическое здравоохранение предполагает обеспечение соответствующего уровня квалификации добровольцев. Решением данного вопроса представляются подготовка и переподготовка больничных волонтеров и специалистов различных уровней на базе медицинских образовательных организаций. Обучение младших медицинских сестер по уходу за больными (сестер милосердия) в Ярославском государственном медицинском университете началось в 2023 г. В ЯГМУ была создана базовая кафедра паллиативной медицины на базе АНО ЦКБ Святителя Алексия Митрополита Московского Московской Патриархии Русской Православной Церкви. Взаимодействие с государственными, общественными и конфессиональными структурами позволяет решать вопросы практической реализации волонтерами полученных навыков с учетом широкого диапазона запросов общества.

Ключевые слова: больничное добровольчество, социальная инициатива, сестры милосердия, Ярославский государственный медицинский университет

Вклад авторов: А. Л. Хохлов, П. С. Жбанников, А. Ю. Заров, Д. Е. Фирсов, А. В. Шкуранков, С. В. Макаров — сбор статистических данных, подготовка текста.

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

Статья поступила: 06.10.2023 **Статья принята к печати:** 15.11.2023 **Опубликована онлайн:** 29.12.2023

DOI: 10.24075/medet.2023.027

In the modern world, social service is not only relevant, it also acquires new actual forms. It is equipped with technological abilities, adapts to the changing standards of life quality and increasing society demands. Meanwhile, the conceptual volunteering basis behind these initiatives, which rests on the universal principles of humanism and tender mercy, remains unchanged.

In practical healthcare, the socially-oriented initiative can be applied as well. Meanwhile, in medical practice, the traditions of volunteering preserved the most historically demanding form of direct interaction between a trained volunteer and a patient to provide additional labor-intensive care. The experience of hospital service is still particularly relevant in relation to palliative patients. The relevance of hospital service is accepted by the professional medical society, translated into the information space, and positively perceived by the entire society [1].

The problem is that volunteers who are massively attracted to accomplish the tasks of nursing staff require proper qualification. They should not only be motivated for social service but also have special knowledge, which allows to integrate everyday patient care into the structure of medical aid.

The issue is solved by training and retraining of hospital volunteers and specialists of various levels on the basis of medical educational institutions.

Training of nurses (nurses of mercy) was organized at the Yaroslavl State Medical University to meet the growing need of practical healthcare in support of volunteering initiatives.

A step preceding implementation of this educational program included creation of the basic department of palliative medicine on the basis of Clinical Central Hospital of St. Alexy Metropolitan of Moscow of the Moscow Patriarchate of the Russian Orthodox Church at the Yaroslavl State Medical University (Moscow, head of the department, Director and Head Physician of Clinical Central Hospital Zarov AYu). The experience of successful training at the Clinical Central Hospital of St. Alexy Metropolitan of Moscow was taken as the basis of organization of educational process at the Yaroslavl State Medical University. Specialists of the Clinical Central Hospital actively participated in practical implementation of educational programs.

Training of 'nurses of mercy' at the Yaroslavl State Medical University started at the same time with the Sretensky Readings devoted to the memory of Saint Luke (Voino-Yasenetsky) [2]. Representatives of the medical corporation, specialists of the social sphere and priests met at the conference to discuss the pressing issues of palliative medicine in Russia. Discussing the joint perspectives of healthcare, society and church was the major topic of presentation. Participation of the confessional community showed the importance of discussing the issue of physical comfort, spiritual and moral upbringing of palliative patients.

The educational project gained a regional significance due to the interaction of the Yaroslavl State Medical University, Ministries of Healthcare, Labor and Social Support of the Yaroslavl region, and Yaroslavl Diocese of the Russian Orthodox Church.

It should be noted that the students of the Yaroslavl State Medical University were the first to take the initiative for obtaining additional volunteering competency. In 2023, the 'junior medical nurse' (training) program at the Yaroslavl State Medical University was mastered by 11 students enrolled in 'Clinical Psychology' specialty program, 22 volunteers recommended by the Yaroslavl Diocese of the Russian Orthodox Church, and 60 students of social welfare bodies within the pilot project devoted to the system of long-term care for elder citizens and persons with disabilities in need of care.

The 'junior medical nurse' professional training program at the Yaroslavl State Medical University was implemented in accordance with art. 73 of Federal Law as of 29.12.2012 No. 273-FZ 'On education in the Russian Federation', Law of the Ministry of Education of Russia as of 26.08.2020 No. 438 'On approved procedure of organization and carrying out the educational activity for the basic programs of professional education', and Rules of admission set by the University.

The training program lasts 432 hours and consists of five modules.

1. Theory and practice of nursing care.
2. Safe patients and personnel environment.
3. Technologies of rendering medical services.
4. Practical training — mastering practical skills at the accreditation and simulation center.
5. Production practice (training at a medical organization).

Following completion of the training, a qualifying exam is held in the presence of the employer's representatives.

The volume of practical training (simulation course within the framework of your studies, production practice and practical classes) takes up more than 90% of class time.

Social request of profile regional ministries and Yaroslavl Diocese of the Russian Orthodox Church allowed to take into account the target of the future activity, and specifics of confessional and cultural environment while training specialists and volunteers.

It can be concluded that referral to the experience of hospital volunteering and traditions of tender mercy has shown the critical need of the modern Russian medicine for the search of additional resources to provide qualitative patient care, especially for palliative patients, on the one hand, and the spiritual need of the society for the development of social initiatives, on the other hand.

Training of junior nurses ('nurses of mercy') at the Yaroslavl State Medical University proves that it is possible to restore practice of hospital volunteering in Russian healthcare with integrated efforts of all interested parties.

The area of further practical implementation of skills obtained by volunteers is expanded due to the interaction between the university and state, social, and confessional structures. It also allows to take into account the specifics of their requests and peculiarities of the worldviews, which, in its turn, simulates the interest of students in the educational program.

According to practical experience, 'tender mercy' is the initiative, which is gaining popularity in contemporary society. However, all interested parties should take part herein to ensure its complete implementation. The reciprocal activity associated with the development and implementation of courses by the academic society and willingness of the higher medical school to include the tasks supporting the practice of hospital volunteering in the perspective plan of development are essential.

Results of the first year of junior nurse training at the YSMU demonstrate that the Yaroslavl Diocese, social welfare bodies and medical organizations display a stable interest in implementation of the program.

The motto of the Sretensky Readings devoted to the memory of Saint Luke (Voino-Yasenetsky), which launched the initiative of the Yaroslavl State Medical University, is 'Education, Health, and Mercy'. It reflects the readiness to consolidate the efforts of the representatives of medical education and practical healthcare, secular society and confessional associations to solve common pressing social tasks.

References

1. Yaroslavskiy meduniversitet nachal podgotovku sester miloserdiya dlya pomoshchi tyazhelo bol'nym. Available from URL: https://tass.ru/v-strane/17025979 Russian.
2. «Sretenskiye chteniya», posvyashchennyye razvitiyu palliativnoy meditsiny v Rossii. Available from URL: https://ysmu.ru/press-center/news/2023/sretenskie-chteniya-v-yaroslavskom-gosudarstvennom-meditsinskom-universitete/ Russian.

Литература

1. Ярославский медуниверситет начал подготовку сестер милосердия для помощи тяжело больным. Режим доступа: [Электронный ресурс]. URL: https://tass.ru/v-strane/17025979
2. «Сретенские чтения», посвященные развитию паллиативной медицины в России. Режим доступа: [Электронный ресурс]. URL: https://ysmu.ru/press-center/news/2023/sretenskie-chteniya-v-yaroslavskom-gosudarstvennom-meditsinskom-universitete/

MEDICINAL PRODUCT EARLY ACCESS PROGRAMS: EXPERIENCE OF THE BRICS GROUP, EUROPEAN UNION, AND UNITED STATES OF AMERICA

Omelyanovskiy VV[1,2], Rukavitsyna NP[1] ✉, Mukhortova PA[1], Kingshott AA[1,2], Zinadinov SI[1], Kharitonova AG[1,3], Minakova EI[1], Krekhtunova LO[1], Barysheva VO[1,2]

[1] Center for Healthcare Quality Assessment and Control, Moscow, Russia

[2] Russian Medical Academy of Continuous Professional Education, Moscow, Russia

[3] First Moscow State Medical University named after Sechenov IM (Sechenov University), Moscow, Russia

Timely accessibility of effective and safe medicinal products is one of the main tasks of healthcare. The goal of the present review is to assess various approaches that provide an early access to medicinal products within the BRICS group (list of participants as of 01.10.2023), European Union and United States of America. The stage of the life cycle of medicinal products is closely associated with their further movement in the market, patient access rate, and partially with the issues of their financing and reimbursement, which directly influence their affordability for population. The article contains data about the specifics of expanded access to unregistered medicinal products used on a compassionate basis and presenting therapy under early access programs financed by pharmaceutical companies; it also describes approaches to accelerated registration and registration of medicinal products in case of limited clinical data. Experience of the reviewed countries in early access programs is described.

Key words: regulatory approval of drugs, compassionate use, expanded access, expedited access, accelerated expertise, conditional registration, scientific advice, breakthrough therapy, technology transfer

Author contribution: Omelyanovskiy VV — text editing, preparing the manuscript for publication; Rukavitsyna NP — review of publications related to the article topic (RF, USA), writing an article, text editing, preparing the manuscript for publication; Mukhortova PA — review of publications related to the article topic (RF, EU), writing sections, text editing; Kingshott AA — writing an abstract, writing an article, text editing, preparing the manuscript for publication; Zinadinov SI — review of publications related to the article topic (South Africa), writing text sections (South Africa) and text editing; Kharitonova AG — review of publications related to the article topic (India), writing sections (India), text editing, preparing the manuscript for publication; Minakova EI — review of publications related to the article topic (Brazil), writing sections of the (Brazil) and text editing Krekhtunova LO — review of publications related to the article topic (China), writing text sections (China), text editing, preparing the manuscript for publication; Barysheva VO — text editing.

✉ **Correspondence should be addressed:** Nadezhda P. Rukavitsyna
Khokhlovsky per., 10, str.5, Moscow, 109028, Russia; rukavitsyna@rosmedex.ru

Received: 31.10.2023 **Accepted:** 12.11.2023 **Published online:** 27.11.2023

DOI: 10.24075/medet.2023.029

ПРОГРАММЫ РАННЕГО ДОСТУПА ЛЕКАРСТВЕННЫХ ПРЕПАРАТОВ: ОПЫТ БРИКС, ЕВРОПЕЙСКОГО СОЮЗА, СОЕДИНЕННЫХ ШТАТОВ АМЕРИКИ

В. В. Омельяновский[1,2], Н. П. Рукавицына[1] ✉, П. А. Мухортова[1], А. А. Кингшотт[1,2], С. И. Зинадинов[1], А. Г. Харитонова[1,3], Е. И. Минакова[1], Л. О. Крехтунова[1], В. О. Барышева[1]

[1] Центр экспертизы и контроля качества медицинской помощи, г. Москва, Россия

[2] Российская медицинская академия непрерывного профессионального образования, Москва, Россия

[3] Первый Московский государственный медицинский университет имени И. М. Сеченова (Сеченовский университет), г. Москва, Россия

Одной из основных задач здравоохранения является обеспечение своевременной доступности эффективных и безопасных лекарственных препаратов населению. Цель настоящего обзора заключается в оценке различных подходов, обеспечивающих ранний доступ к лекарственным препаратам в странах БРИКС (список участников по состоянию на 01.10.2023), а также в Европейском Союзе и Соединенных Штатах Америки. Данный этап жизненного цикла лекарственных препаратов тесно связан с дальнейшей траекторией их движения на рынке и скоростью доступа пациентам, а также отчасти и с вопросами финансирования и возмещения, которые напрямую определяют их доступность населению. В статье приведена информация об особенностях расширенного доступа для незарегистрированных лекарственных препаратов в рамках сострадательного использования и предоставления терапии в рамках программ раннего доступа, финансируемым фармацевтическими компаниями, а также отображены подходы ускоренной регистрации и регистрации лекарственных препаратов при ограниченных клинических данных. Описаны практики рассматриваемых стран по программам раннего доступа.

Ключевые слова: регистрация лекарственных препаратов, сострадательное использование, расширенный доступ, ускоренный доступ, ускоренная экспертиза, условная регистрация, научное консультирование, прорывная терапия, трансфер технологий

Вклад авторов: Омельяновский В. В. — редактирование текста, подготовка рукописи для публикации; Рукавицына Н. П. — обзор публикаций по теме статьи (РФ, США), написание текста статьи, редактирование текста, подготовка рукописи для публикации; Мухортова П. А. — обзор публикаций по теме статьи (РФ, ЕС), написание разделов, редактирование текста; Кингшотт А. А. — составление резюме, написание текста статьи, редактирование текста, подготовка рукописи для публикации; Зинадинов С. И. — обзор публикаций по теме статьи (ЮАР), написание разделов текста (ЮАР) и редактирование текста; Харитонова А. Г. — обзор публикаций по теме статьи (Индия), написание разделов текста (Индия), редактирование текста, подготовка рукописи для публикации; Минакова Е. И. — обзор публикаций по теме статьи (Бразилия), написание разделов текста (Бразилия) и редактирование текста; Крехтунова Л. О. — обзор публикаций по теме статьи (КНР), написание разделов текста (КНР), редактирование текста, подготовка рукописи для публикации; Барышева В. О. — редактирование текста.

✉ **Для корреспонденции:** Надежда Петровна Рукавицына
Хохловский пер., д. 10, стр. 5, г. Москва, 109028, Россия; rukavitsyna@rosmedex.ru

Статья поступила: 31.10.2023 **Статья принята к печати:** 12.11.2023 **Опубликована онлайн:** 27.11.2023

DOI: 10.24075/medet.2023.029

Population health is a priority of state policy around the globe. Timely provision medicines is a key task of healthcare [1]. Development and launching original medicines to the market is associated with enormous labor, time and resource expenditures. It may take 10–15 years to register a new molecule after its discovery, whereas the costs may vary from 160 million US dollars to 4.56 billion US dollars depending on the therapeutic use and specifics of medicines manufacture [2]. So, many years of medicinal product development and launching will pass before patients are able to use it.

In the global practice, there exist different methods of accelerated access to innovative and specifics of medicines manufacture [2] within the most important nosologies under early access programs. The following directions can be identified here:

1. **Making medicines accessible prior to commercial circulation (expanded access/compassionate use) [3].**
2. **Accelerated access during registration procedures:**
   a. Scientific counseling at different pre-marketing stages of medicines life cycle;
   b. Shorter term of registration procedures;
   c. Mechanisms of registration based on limited clinical data.

The goal of these programs is to provide the necessary therapy to patients, on the one hand, and make the therapy safe and effective, on the other hand. It should be noted that medicines become accessible to population to the necessary extent only following approval for public funding. Today, the issue of access to novel medicines at the national level is mainly raised during post-marketing period. They can also be reviewed to ensure subsequently accelerated implementation of access into clinical practice. The early access measures reviewed in the article constitute the first stage of provision of patients with required medicines.

Within the review, various practices providing a faster access of medicines to the market of Russia and BRICS (Brazil, Russia, India, China, South Africa; an international unity of five countries such as Brazil, Russia, India, China, South Africa), European Union (EU) and United States of America (USA) will be provided.

EXPANDED ACCESS PROGRAMS (COMPASSIONATE USE):

Expanded access, which is also called ‘compassionate use’, makes it possible to use the medicines at different stages of its life cycle. The expanded use programs can provide patients with medicines utilized during clinical studies (CS) or medicines that were assessed as effective and safe during the CS but with pending requests for registration or medicines with pending permission for authorization after the registration was approved. Thus, these programs allow patients to use unregistered medicines, medicines registered prior to approval for commercial circulation and, in some countries, prior to approval for remuneration. Compassionate use programs can be used only in relation to those medicines that can help patients with life-threatening, long-term or severely disabling diseases with no current therapy available or with an unsatisfied medical need [3, 4, 5].

It should be noted that expanded use programs differ from CS mainly by the goal of providing a patient with the required therapy taking into account the unmet medical need. The goal does not involve collection of information related to therapy effectiveness as it is done during a CS. Therapy-related adverse effects should be recorded within the rules of pharmacovigilance, and, in some cases, while providing access medicines under the expanded use programs sponsored by pharmaceutical companies; data related to effectiveness and safety of medicines are additionally collected to ensure its further market promotion [6]. A doctor deals with the primary appointment of medicines to a patient based on a clinical situation, whereas a regulatory body in every country delivers a resolution regarding the possible import of an unregistered drug and its use by a patient. The expanded access program can be initiated by a doctor or a group of doctors or an authorized national regulatory body [3, 4]. Meanwhile, an ethical committee can be involved into taking a decision about the necessary medicines provision under the expanded access program in some countries only (USA, Spain and Italy) [7].

Various expanded access programs depend on the country where they are used and are divided as follows:

- allow the use of unregistered medicines within a certain cohort/group of patients (USA, Germany);
- allow the use among individual patients (BRICS, many countries within the EU, USA).

It should be noted that the expanded access programs are presented within all analyzed countries [3, 8, 9, 10, 11]. For instance, import of unregistered medicines to Russia for patients or a group of patients is possible in the presence of a decision issued by a medical commission and import permit issued by an authorized federal executive agency based on the corresponding application [12]. In India, import of unregistered medicines to treat patients is possible based on the personal application from a patient or a hospital. For instance, the mechanism was implemented to provided patients with resistant tuberculosis with bedaquiline and delamanid [13]. In Brazil, an additional early access program for innovative drugs was introduced. This made it possible to continue previous therapy after CS completion but prior to medicines registration in the country [14, 15, 16].

EXPANDED PROGRAMS

No similar regulatory systems exist for today. However, in the examined countries the expanded procedures often overlap both terminologically (in the name), and by the approaches used. It should be noted that though some names overlap, the programs do not have a semantic identity (fig).

SCIENTIFIC COUNSELING AT DIFFERENT PRE-MARKETING STAGES OF MEDICINES LIFE CYCLE;

As Russian is a member of the Eurasian Economic Union (EEU), scientific and pre-marketing consultations by authorized bodies or expert organizations of member states are set by article 26 of Decision No. 78 as requested by the applicant. Consultations are provided prior to submission of marketing authorization for medicines regarding the issues related to analytical studies, preclinical and clinical studies, aspects of registration procedures, etc. A center of medical technology transfer was created in Russia while implementing the project entitled Human-Oriented Medical Science. Its goal is to assist developers of drug and methods of health protection [17].

Scientific counselling is practiced in Brazil, South Africa, and China by the main authority regulating drug circulation. The goal of consultation with the respective authority is to review and agree upon the application format and discuss technical matters of dossier submission and registration approaches [18, 19, 20].

The USA and EU have the longest review experience in scientific counselling. Scientific counselling is done by the FDA (USA) since 2009 and by EMA (EU) since 1995. Moreover,

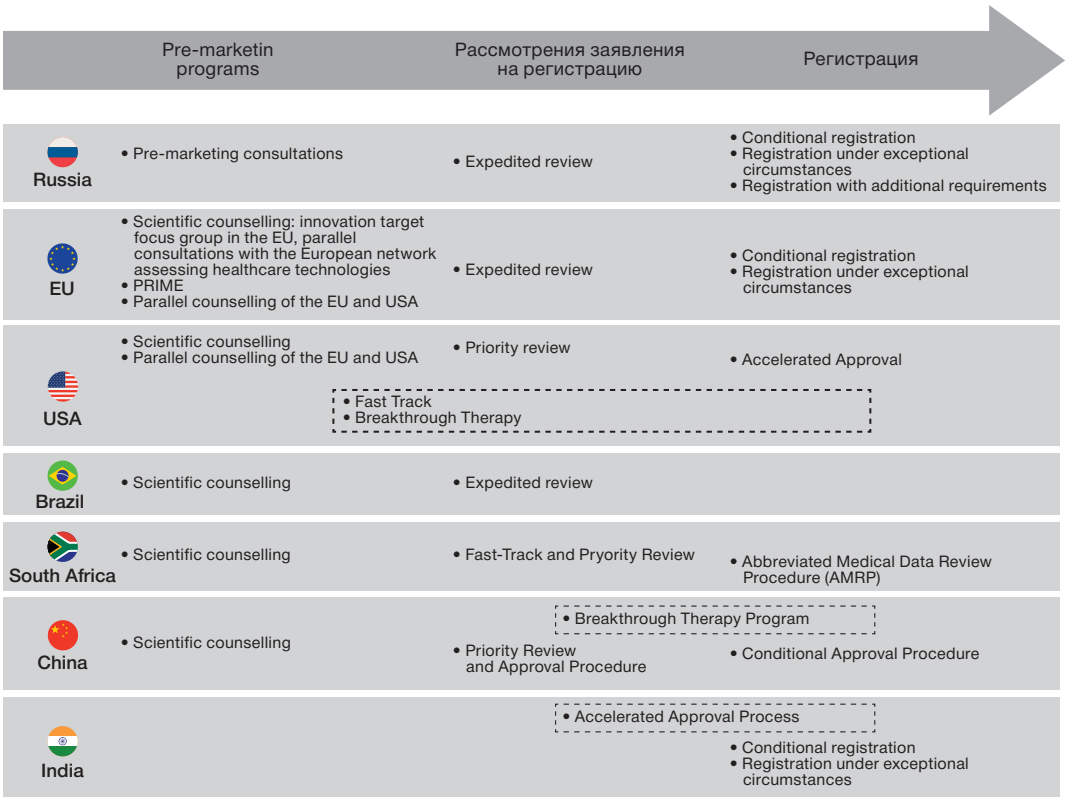

Fig. Accelerated access programs in the BRICS group, European Union (EU), United States of America (USA) (programs combining several approaches are shown with dashed lines)

parallel counselling with two agencies (EMA and FDA) is available since 2006 [21].

FDA practices four types of counselling with certain issues to be discussed during each of it [22].

The Innovation Task Force (ITF) makes it possible to have an informal early dialogue with applicants [23].

Since 2016, the *PRIME* program has been used to support the development of drugs intended for therapy of diseases with no current therapeutic options available. The program allows for extended interaction and early dialogue with developers of perspective drugs to optimize the plans of development and accelerate assessment during registration [24]. The results show that successful conditional registration of 8 drugs under the PRIME program was possible 3.75 years earlier as compared to standard registration [25].

It should also be noted that parallel counselling of EMA and European Network for Health Technology Assessment, (EUnetHTA) have been possible since July 2017. The procedure replaces the scientific counselling by EMA and EUnetHTA when developers of drugs had to refer to European Agencies for Health Technology Assessment on the individual basis. The counselling results are used later to inform of reimbursement of treatment expenses and of price of the approved drug at the national level [26].

PROGRAMS WITH REDUCED INTERVALS OF REGISTRATION PROCEDURES.

Direct reduction of registration intervals is one of the most obvious options that accelerate access of patients to medicines.

In the USA, the option is used in the priority review program *when* the application is reviewed (accelerated check by the FDA of how the application for a new drug is filled in) during 6 months as compared with 10 months while performing a standard examination.

The program, if it is participated, can be completed with the *Fast Track*. The goal of this program is to develop and accelerate the process of registration of drugs to treat serious diseases and intended for use within the area of unsatisfied medical needs.

As soon as the drug is assigned Fast Track, it is possible to use the program preferences such as

1) consultations with the regulating authority (FDA);
2) participation in the program of **accelerated approval** (presented below);
3) reduced interval of registration procedures due to the consistent review and possible participation in the priority review program [27].

In the EU, the program is accessible when the programs of drug registration based on limited data are combined with an accelerated review of drugs during the registration. EMA suggests that very essential drugs should undergo through the accelerated review (150 days). A standard centralized procedure can last for up to 210 days (not taking into account the time intended for submitting additional data by the applicant) [28].

In the BRICS group, the programs of accelerated access are of different types. In Russia, the situation reminds of EU-based approaches. The program is accessible when the drug accelerated review is combined with the programs of drug registration based on limited data. According to Decision No. 78, since 2022 an accelerated expertise can be used during the registration of orphan, pediatric medicines and medicines, which are especially important for the health of the population, with registration in a reference state for no more than 100 working days, which is 40 working days less than in case when standard registration procedures are applied [29].

In Brazil, medicines undergo through the procedure of accelerated approval regulated by resolution RDC 204/2017 for common nosologies (the selection criterion is hard-to-treat

diseases, conditions that occur in the result of urgent situations, neglected tropical diseases, etc.) and resolution RDC 205/2017 for orphan diseases. The period of CS registration can be reduced to 60 days [30, 31].

In India, it's called **an Accelerated Approval Process.** Under the program, medicines have reduced terms of registration and it's possible to use clinically sound surrogate endpoints. The type of data required by the Central Drug Standard Control Organization (CDSCO) to take a decision depends on the stage of medicines development. When the pandemic occurred, several COVID-19 vaccines were registered in the country under the program [32, 33].

In China, they used the **Priority Review and Approval Procedure to accelerate the registration process.** Shorter terms of review allow to reduce the waiting period while filing an application for marketing authorization. The National Medical Products Administration (NMPA) and Center for Drug Evaluation (CDE) [34] belong to the regulating authorities. Medicinal preparations for emergency care, innovative and many other medicines indicated by NMPA can participate in the program [35].

Two similar early access programs (Expedited review process, Fast-Track) and Priority Review are available in South Africa. Their goal is to accelerate the registration of some medicines with an important therapeutic effect. They have to be urgently acquired to solve the basic healthcare problems. Fast-Track is regulated by the Medicines Control Council (MCC). The procedure is valid for the medicines included into Essential Drugs List (EDL) and novel chemical compounds which are essential for national healthcare but are not on the List. Priority Review is regulated by the South African Health Product Regulatory Authority (SAHPRA). It applies to the medicines which replenish a non-satisfied medical need, show a significant therapeutic advantage related to safety and effectiveness as compared to the existing therapy options; medicines to treat conditions and orphan diseases which are life-threatening or cause serious complications; medicines used in case of emergencies in public healthcare and animal health; medicines that constitute a national priority determined by the National Healthcare Ministry.

The target time for consideration of applications issued under the program is 250 calendar days [36, 37]. It should be noted that the average time for consideration of expedited applications approved in 2015, 2016 and 2017 amounted to 1218, 921 and 609 calendar days respectively [36].

Another expedited access program occurring in the USA and China is represented by **Breakthrough Therapy** *in the USA* **and Breakthrough Therapy Drug Procedure (BTD)** *in China*. It accelerates development and review of innovative drugs aimed at the prevention and treatment of serious diseases dangerous for life or diseases significantly influencing the quality of life when no effective options of prevention and therapy are available.

In the USA, both pharmaceutical companies, and the FDA can initiate the program. Under the program, the preliminary clinical data should inform that medicines has significant advantages as compared to the affordable therapy in relation to the clinically significant endpoint (endpoints) [38].

Spesolimab (SPEVIGO) is an example of the drug registered in 2022 under the program. It is used to treat exacerbated generalized pustular psoriasis in adults. It is the first medicines approved for treatment of the nosology [39].

In China, it is required to obtain recommendations from CDE (NMPA) during a CS via a special interaction channel (it reduces possible risks and allows for better understanding of the expectations of a regulating authority); the right of the studied medicines for priority review while filing an application for marketing authorization (significantly reduces the review period reduces the time spent on clinical development and approval of a marketing authorization [35].

Thus, all the countries mentioned herein provide for a shorter registration period under the individual or combined programs for certain groups of medicines.

THE REGISTRATION PROGRAMS BASED ON LIMITED CLINICAL DATA

The next group of programs accelerating access of patients to medicines is aimed at the possible use during registration of somehow limited clinical data on effectiveness and/or safety, and when it is impossible to present them at all (in case of orphan diseases) or due to unfinished CS.

In the USA, the option is provided under the program of **accelerated approval**. The goal is to ensure access of medicines to the market based on surrogate outcomes, which are considered justified regarding the probable benefit for a patient. It makes it possible to accelerate the CS by allowing to complete the trials before severe clinical outcomes occurred. In 2022, the program was used to register adagrasib to treat adult patients with progressing or metastatic non-small cell lung carcinoma in the presence of KRAS G12C mutation. Indication for this medicines was approved based on such outcome-related results as tumour response rate and duration of response. Whether the medicines will be subsequently used depends on the outcomes that confirm the studies [40].

In the EMA, there exist two related programs depending on the possibility to present complete data after medicines registration, — **conditional registration and registration under exceptional circumstances**. The first one is applied when the total volume of data are planned to be presented following registration (for instance, following completion of a CS). The following medicines can be registered [41]:

- medicines intended for treatment, prevention or medical diagnostics of severe debilitating diseases or life-threatening diseases;
- medicines intended to be used in emergency situations that threaten the public health;
- orphan medicines.

Over the 10-year period of the program (2006–2016), 30 marketing authorizations were registered under the conditional registration; 11 of them were standard, 2 were withdrawn for commercial reasons, whereas 17 remained conditional [41].

Just as in case with any medicines, if according to new data the drug benefit outweighs the risk, the EMA can accept the regulatory measures and, for instance, stop or withdraw sale permit[41]. Registration can be terminated based on an applicant's decision (following commercial reasons). Thus, betibeglogene autotemcel (ZYNTEGLO) to treat beta-thalassemia was conditionally registered in 2019. The initial duration of action for conditional registration was 1 year. Later the registration was prolonged for 1 more year in 2020 and 2021. However, in 2022, Bluebird Bio BV notified the European Commission that the permit for its sale is terminated permanently due to commercial reasons [42].

Registration under exceptional circumstances is possible in the following cases:

- Prevalence of therapeutic indication is so low that it is impossible to expect exhaustive data from the applicant;
- no exhaustive data can be presented taking into account the current condition of scientific knowledge;

– collection of data contradicts the general principles of medical ethics.

Thus, registration under exceptional circumstances differs from conditional registration because conditional registration means addition of data as soon as the CS is over and in case of subsequent replacement of conditional registration with standard one, whereas registration under exceptional circumstances doesn't require addition of data [28].

Defibrotide (DEFITELIO) is a medicinal preparation registered under exceptional circumstances and used to treat severe vein occlusion among patients who underwent haematopoietic stem cell transplantation. Though a comparative placebo-controlled study can't be carried out, a company compared it with the historical control when effectiveness of the assumed preparation was proved taking general survival into account [5].

In Russia, supranational law contains the following programs of a similar type:

1) registration of medicines with establishment of additional requirements;
2) registration of medicines under exceptional circumstances;
3) conditional registration of medicines.

Thus, a possible **additional requirement** can include post-marketing studies of drug safety and, if required, a study of various aspects of drug effectiveness, which can't be examined prior to drug marketing.

In Russia, approaches to drug registration **under exceptional circumstances** (applicant as an initiator) and **conditional registration** (applicant or an authorized body (expert company) of a reference state as an initiator) are similar to the principles used in the EU. Health-related benefit associated with immediate registration of all mentioned medicines should outweigh the risks related to the delay of the additional data [29].

Tisagenlecleucel (Kymriah) was the first high-tech medicinal product registered under the program of conditional registration for CAR-T-cell therapy in oncology [43].

In India, **conditional registration** is done under the initiative of the sponsor or applicant. It is also applied to those medicines, which are used with a significant decrease in the rate of adverse reactions that restrict treatment and with an increase of patient compliance, which, as it was expected, could lead to an accelerated achievement of clinically important outcomes. However, orphan drugs should undergo through an accelerated expertise; it is allowed that the results obtained during some (not all) phases of CS can be presented. Further presentation of results of post-marketing studies is an obligatory condition. CDSCO assesses the presented information just like in case with other programs of accelerated registration [32, 44].

Analogous program of medicines registration **under exceptional circumstances** is available in India. It applies to medicines, which are developed to be used under exceptional circumstances. The program is used at the request of a sponsor or an applicant when preclinical data confirm that the preparation is effective, when it is impossible to conduct a CSCT and when there exists a common therapeutic strategy. The approval can be used only once. It can be prolonged only when a detailed report about effectiveness of this intervention was prepared [32].

In China, **the Conditional Approval Procedure** allows to have more frequent meetings with regulatory bodies, reduce the length of submission and obtain approval based on surrogate endpoints or non-comparative studies until the confirmatory testing is completed[45, 46]. medicines can be approved if the studies are completed after medicines entrance to the market if the medicines effectiveness will be shown at early stages [47].

In South Africa, medicines can be registered based on incomplete clinical data when the abbreviated medicine review process is applied. A program limiting the time required to assess the pharmaceutical products registered in the countries with SAHPRA-recognised registering authorities (RAA), for instance, USA (FDA), Canada (Ministry of Health) and other bodies provided that the medicines assessment report is easily available [37].

Thus, the idea of using incomplete clinical data somehow presents in all registration systems and allows to significantly accelerate the process of development of and access to various groups of medicines.

ADDITIONAL PROCEDURES

The procedures developed and used by the states in different emergency situations can be considered as additional activities.

In Russia, these are governmental regulations related to the circulation of medicines, which significantly reduced the period required for medicines to get an access to the market (GR No. 441 and 593). It was necessary to adopt these regulations in connection with the WHO coronavirus pandemic (2020) and introduction of restrictive economic measures against the Russian Federation (2022). The abovementioned regulations make registration, which is carried out by the Ministry of Health of Russia, possible within a term not exceeding 20 working days and 60 working days [48, 49].

In China, **they use the Special Review and Approval Procedure as an additional program**. In case of any public health emergencies, a special review and approval of respective therapeutic and preventive medicinal preparations are carried out based on the NMPA decision. The use of medicines included into a special procedure can be limited in a timely manner taking into account certain requirements for the prevention of and struggle with diseases [35].

In Brazil, when COVID-19 vaccines were launched to the market, the process of the clinical trial application review was reduced from 180 days to 72 hours; the marketing authorization file for the vaccine was reviewed during 60 days instead of 120–360 days [50].

CONCLUSION

Improved and accelerated access to drug-induced therapy plays an important role in treatment of patients with life-threatening diseases and/or diseases that significantly reduce the quality of life. Unregistered medicines can be provided in all countries on the compassionate use basis irrespective of any existing limitations in the development of legal documents. Mechanisms supporting medicines development and registration using the shorter application term and registration based on a limited number of data make it possible to reduce the time prior to approval significantly. Meanwhile, the regulatory bodies use various additional measures to control effectiveness and safety of these medicines. Expedited and/or conditional registration is possible in all the mentioned countries. However, their number, variety and additional requirements for medicines by regulators are mainly determined by the social and economic context of the analyzed countries. The current practice shows that early scientific counseling is essential. It should be implemented both by the regulatory authorities issuing recommendations about the registration of medicines and agencies assessing healthcare technologies for their subsequent implementation into the clinical practice and taking decisions regarding state financing and getting a real access to medicines for patients.

References

1. Prikaz Ministerstva zdravookhraneniya RF ot 13.02.2013 N 66 (red. ot 13.07.2021) “Ob utverzhdenii Strategii lekarstvennogo obespecheniya naseleniya Rossiyskoy Federatsii na period do 2025 goda i plana ee realizatsii”. Konsul’tantPlyus.
2. Schlander M, Hernandez-Villafuerte K, Cheng CY, Mestre-Ferrandiz J, Baumann M. How Much Does It Cost to Research and Develop a New Drug? A Systematic Review and Assessment. Pharmacoeconomics. 2021; 39 (11):1243–1269. PubMed PMID: 34368939.
3. Watson T. A Global Perspective on Compassionate Use and Expanded Access. Ther Innov Regul Sci. 2017; 51 (2): 143–145. PubMed PMID: 30231725.
4. Patil S. Early access programs: Benefits, challenges, and key considerations for successful implementation. Perspect Clin Res. 2016; 7 (1): 4–8. PubMed PMID: 26955570.
5. EMA. Defitelio. European Medicines Agency. 2018. Available from URL: https://www.ema.europa.eu/en/medicines/human/EPAR/defitelio (accessed: 05.06.2023).
6. Sarp S, Reichenbach R, Aliu P. An approach to data collection in compassionate use/managed access. Front Pharmacol. 2022; 13:1095860. PabMed PMID: 36605403.
7. Borysowski J, Ehni HJ, Górski A. Ethics review in compassionate use. BMC Med. 2017; 15 (1): 136. PabMed PMID: 28735571.
8. Questions and answers on the compassionate use of medicines in the European Union. Available from URL: https://www.ema.europa.eu/en/documents/other/questions-answers-compassionate-use-medicines-european-union_en-0.pdf (accessed: 09.03.2023).
9. Han B, Ji J, Zhang B, Bai H, Zhou D, Feng F, et al. The first successful expanded compassionate use of Iptacopan in a patient with paroxysmal nocturnal hemoglobinuria. Ann Hematol. 2022; 101 (11): 2537–2539. PubMed PMID: 35965286.
10. Act to provide for the registration of drugs intended for hnman nse, Government gazette extraordinary № 1171, 1965.
11. Jarow JP, Lurie P, Ikenberry SC, Lemery S. Overview of FDA’s Expanded Access Program for Investigational Drugs. Ther Innov Regul Sci. 2017 Mar 1;51(2):177–179. PubMed PMID:28553565.
12. Federal’nyy zakon ot 12.04.2010 N 61-FZ (red. ot 04.08.2023) “Ob obrashchenii lekarstvennykh sredstv” (s izm. i dop., vstup. v silu s 01.09.2023), Konsul’tantPlyus.
13. Shetty YC, Brahma S, Manjesh PS. Compassionate drug use: Current status in India. Perspect Clin Res. 2020; 11 (1): 3–7. PMID: 32154142.
14. Expanded Access, Compassionate Use and Post-study Drug Supply Programs in Brazil. Available from URL: https://globalregulatorypartners.com/wp-content/uploads/Expanded-Access-Compassionate-Use-and-Post-Study-Drug-Supply-Programs-Brazil.sd_.pdf
15. Resolution of the Collegiate Board. RDC 38/2013. Available from URL: https://bvsms.saude.gov.br/bvs/saudelegis/anvisa/2013/rdc0038_12_08_2013.html.
16. Resolution of the Collegiate Board. RDC 336/2020. Available from URL: https://www.in.gov.br/en/web/dou/-/resolucao-rdc-n-336-de-30-de-janeiro-de-2020-240823596.
17. Prikaz Ministerstva zdravookhraneniya RF ot 28.01.2022 N 40 “O tsentre transfera meditsinskikh tekhnologiy”. Konsul’tantPlyus.
18. Guideline for pre-registration consultation meeting of 2022, SAHPGL-PEM-BIO-03_v3 (September 15, 2022).
19. Argotti U, Leyens L, Lisbona C, López P, Alonso-Orgaz S, Nevado A, Cozzi V. Comparison of the Latin America Regulation Landscape and International Reference Health Authorities to Hasten Drug Registration and Clinical Research Applications. Ther Innov Regul Sci. 2023 PubMed PMID: 37682461.
20. National Medical Products Administration. Business consultation related to drug registration application communication meeting. Available from URL: https://zwfw.nmpa.gov.cn/web/taskview/11100000MB0341032Y100207203100001.
21. Mel’nikova EV, Merkulova OV, Merkulov VA. Mirovaya praktika nauchnogo konsul’tirovaniya po voprosam razrabotki i registratsii innovatsionnykh preparatov. BIOpreparaty. Profilaktika, diagnostika, lechenie. 2021; 21 (3): 167–177.
22. FDA. Best Practices for Communication Between IND Sponsors and FDA During Drug Development Guidance for Industry and Review Staff Good Review Practice. U. S. Food and drug administrarion. 2017. Available from URL: https://www.fda.gov/media/94850/download (accessed: 05.10.2023).
23. Mandate of the EMA Innovation Task Force (ITF). Available from URL: https://www.ema.europa.eu/en/documents/other/mandate-european-medicines-agency-innovation-task-force-itf_en.pdf (accessed: 05.10.2023).
24. EMA. PRIME: priority medicines. Available from URL: https://www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines (accessed: 05.10.2023).
25. Available from URL: https://www.ema.europa.eu/en/documents/report/prime-analysis-first-5-years-experience_en.pdf.
26. Guidance on Parallel EMA/HTA body (HTAb) Scientific. Advice for the Interim Period. Available from URL: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guidance-parallel-ema/hta-body-htab-scientific-advice-interim-period_en.pdf (accessed: 09.03.2023).
27. FDA. Guidance for Industry Expedited Programs for Serious Conditions — Drugs and Biologics. U. S. Food and drug administrarion. 2023. Available from URL: https://www.fda.gov/files/drugs/published/Expedited-Programs-for-Serious-Conditions-Drugs-and-Biologics.pdf (accessed: 05.10.2023).
28. EMA. Pre-authorisation guidance. European Medicines Agency. 2018. Available from URL: https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/pre-authorisation-guidance (accessed: 11.03.2023).
29. Reshenie Soveta Evraziyskoy ekonomicheskoy komissii ot 03.11.2016 N 78 (red. ot 23.09.2022) “O Pravilakh registratsii i ekspertizy lekarstvennykh sredstv dlya meditsinskogo primeneniya”, Konsul’tantPlyus.
30. Resolution of the Collegiate Board. RDC 204/2017. Available from URL: https://antigo.anvisa.gov.br/documents/10181/2718376/RDC_204_2017_.pdf/b2d4ae64-2d91-44e9-ad67-b883c752c094 (accessed: 09.03.2023).
31. Resolution of the Collegiate Board. RDC 205/2017. Available from URL: https://bvsms.saude.gov.br/bvs/saudelegis/anvisa/2017/rdc0205_28_12_2017.pdf (accessed: 09.03.2023).
32. The draft of the New Drugs and Clinical Trials Rules, 2018, Pub. L. No. D. L.-33004/99 (March 19, 2019).
33. Bishnoi M, Sonker A. Emergency use authorization of medicines: History and ethical dilemma. Perspect Clin Res. 2023;14 (2): 49–55. PubMed PMID: 37325578.
34. Macabeo B, Wilson L, Xuan J, Guo R, Atanasov P, Zheng L, François C, Laramée P. Access to innovative drugs and the National Reimbursement Drug List in China: Changing dynamics and future trends in pricing and reimbursement. J Mark Access Health Policy. 2023; 11 (1): 2218633. PubMed PMID: 37325810.
35. Decree of the State Administration for Market Regulation No. 27. The Provisions for Drug Registration, adopted at the first executive meeting of the State Administration for Market Regulation on January 15, 2020, is hereby promulgated and shall come into force as of July 1, 2020.
36. Keyter A, Banoo S, Salek S, Walker S. The South African Regulatory System: Past, Present, and Future. Front Pharmacol. 2018; 9:1407. PubMed PMID: 30618735.
37. Medicines control council, 2.01_General_information_Jul12_v8_showing_changes.docx (August 2012).
38. Breakthrough Therapy FDA. U. S. Food and drug administrarion. 2018. Available from URL: https://www.fda.gov/patient/fast-track-breakthrough-therapy-accelerated-approval-priority-review/breakthrough-therapy (accessed: 05.10.20).
39. FDA. SPEVIGO®. U. S. Food and drug administrarion. 2022. Available from URL: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761244s000lbl.pdf (accessed: 05.10.2023).
40. Kesselheim AS, Darrow JJ. FDA designations for therapeutics and their impact on drug development and regulatory review outcomes. Clin Pharmacol Ther. 2015; 97 (1): 29–36. PubMed PMID: 25670381.
41. Conditional marketing authorisation Report on ten years of experience at the European Medicines Agency. Available

from URL: https://www.ema.europa.eu/en/documents/report/conditional-marketing-authorisation-report-ten-years-experience-european-medicines-agency_en.pdf (accessed: 09.03.2023).
42. EMA. Zynteglo. European Medicines Agency. 2019. Available from URL: https://www.ema.europa.eu/en/medicines/human/EPAR/zynteglo (accessed: 05.06.2023).
43. YEAES. Kimraya. Available from URL: https://portal.eaeunion.org/sites/commonprocesses/ru-ru/Pages/CardView.aspx?documentId=60dc56f1fb44f1334e36f083&codeId=P.MM.01 (accessed: 06.10.2023).
44. Jain P., Chauhan R. India's New Drugs and Clinical Trials Rules: An Industry Perspective. Regulatory Focus. Regulatory Affairs Professionals Society, 2019.
45. Luo X, Du X, Huang L, Guo Q, Lv X, Wang C et al. Evidence of pre-approval clinical trial supporting the granted conditional approval for novel cancer drugs in China between 2015 and 2022. EClinicalMedicine. 2023; 63: 102177. PubMed PMID: 37662522.
46. Sam Bean. What early access opportunities exist for innovative products in China? 2023.
47. China Adopts Revised Drug Administration Law (September 9, 2019).
48. Postanovlenie Pravitel'stva RF ot 03.04.2020 N 441 "Ob osobennostyakh obrashcheniya lekarstvennykh preparatov dlya meditsinskogo primeneniya, kotorye prednaznacheny dlya primeneniya v usloviyakh ugrozy vozniknoveniya, vozniknoveniya i likvidatsii chrezvychaynoy situatsii i dlya organizatsii okazaniya meditsinskoy pomoshchi litsam, postradavshim v rezul'tate chrezvychaynykh situatsiy, preduprezhdeniya chrezvychaynykh situatsiy, profilaktiki i lecheniya zabolevaniy, predstavlyayushchikh opasnost' dlya okruzhayushchikh, zabolevaniy i porazheniy, poluchennykh v rezul'tate vozdeystviya neblagopriyatnykh khimicheskikh, biologicheskikh, radiatsionnykh faktorov." Konsul'tantPlyus.
49. Postanovlenie Pravitel'stva RF ot 05.04.2022 N 593 "Ob osobennostyakh obrashcheniya lekarstvennykh sredstv dlya meditsinskogo primeneniya v sluchae defektury ili riska vozniknoveniya defektury lekarstvennykh preparatov v svyazi s vvedeniem v otnoshenii Rossiyskoy Federatsii ogranichitel'nykh mer ekonomicheskogo kharaktera." Konsul'tantPlyus.
50. Fast track registration of COVID-19 in Brazil. Available from URL: https://globalregulatorypartners.com/wp-content/uploads/FAST-TRACK-REGISTRATION-OF-COVID-19-VACCINES-IN-BRAZIL.pdf (accessed: 20.09.2023).

Литература

1. Приказ Министерства здравоохранения РФ от 13.02.2013 N 66 (ред. от 13.07.2021) "Об утверждении Стратегии лекарственного обеспечения населения Российской Федерации на период до 2025 года и плана ее реализации". КонсультантПлюс.
2. Schlander M, Hernandez-Villafuerte K, Cheng CY, Mestre-Ferrandiz J, Baumann M. How Much Does It Cost to Research and Develop a New Drug? A Systematic Review and Assessment. Pharmacoeconomics. 2021; 39 (11):1243–1269. PubMed PMID: 34368939.
3. Watson T. A Global Perspective on Compassionate Use and Expanded Access. Ther Innov Regul Sci. 2017; 51 (2): 143–145. PubMed PMID: 30231725.
4. Patil S. Early access programs: Benefits, challenges, and key considerations for successful implementation. Perspect Clin Res. 2016; 7 (1): 4–8. PubMed PMID: 26955570.
5. EMA. Defitelio European Medicines Agency. 2018. Режим доступа: [Электронный ресурс]. URL: https://www.ema.europa.eu/en/medicines/human/EPAR/defitelio (дата обращения: 05.06.2023).
6. Sarp S, Reichenbach R, Aliu P. An approach to data collection in compassionate use/managed access. Front Pharmacol. 2022; 13:1095860. PabMed PMID: 36605403.
7. Borysowski J, Ehni HJ, Górski A. Ethics review in compassionate use. BMC Med. 2017; 15 (1): 136. PabMed PMID: 28735571.
8. Questions and answers on the compassionate use of medicines in the European Union. Режим доступа: [Электронный ресурс]. URL: https://www.ema.europa.eu/en/documents/other/questions-answers-compassionate-use-medicines-european-union_en-0.pdf (дата обращения: 09.03.2023).
9. Han B, Ji J, Zhang B, Bai H, Zhou D, Feng F, et al. The first successful expanded compassionate use of Iptacopan in a patient with paroxysmal nocturnal hemoglobinuria. Ann Hematol. 2022; 101 (11): 2537–2539. PubMed PMID: 35965286.
10. Act to provide for the registration of drugs intended for hnman nse, Government gazette extraordinary № 1171, 1965.
11. Jarow JP, Lurie P, Ikenberry SC, Lemery S. Overview of FDA's Expanded Access Program for Investigational Drugs. Ther Innov Regul Sci. 2017 Mar 1;51(2):177–179. PubMed PMID:28553565.
12. Федеральный закон от 12.04.2010 N 61-ФЗ (ред. от 04.08.2023) "Об обращении лекарственных средств" (с изм. и доп., вступ. в силу с 01.09.2023). КонсультантПлюс.
13. Shetty YC, Brahma S, Manjesh PS. Compassionate drug use: Current status in India. Perspect Clin Res. 2020; 11 (1): 3–7. PMID: 32154142.
14. Expanded Access, Compassionate Use and Post-study Drug Supply Programs in Brazil. Режим доступа: [Электронный ресурс]. URL: https://globalregulatorypartners.com/wp-content/uploads/Expanded-Access-Compassionate-Use-and-Post-Study-Drug-Supply-Programs-Brazil.sd_.pdf
15. Resolution of the Collegiate Board. RDC 38/2013. Режим доступа: [Электронный ресурс]. URL: https://bvsms.saude.gov.br/bvs/saudelegis/anvisa/2013/rdc0038_12_08_2013.html.
16. Resolution of the Collegiate Board. RDC 336/2020. Режим доступа: [Электронный ресурс]. URL: https://www.in.gov.br/en/web/dou/-/resolucao-rdc-n-336-de-30-de-janeiro-de-2020-240823596.
17. Приказ Министерства здравоохранения РФ от 28.01.2022 N 40 "О центре трансфера медицинских технологий". КонсультантПлюс.
18. Guideline for pre-registration consultation meeting of 2022, SAHPGL-PEM-BIO-03_v3 (September 15, 2022).
19. Argotti U, Leyens L, Lisbona C, López P, Alonso-Orgaz S, Nevado A, Cozzi V. Comparison of the Latin America Regulation Landscape and International Reference Health Authorities to Hasten Drug Registration and Clinical Research Applications. Ther Innov Regul Sci. 2023 PubMed PMID: 37682461.
20. National Medical Products Administration. Business consultation related to drug registration application communication meeting. Режим доступа: [Электронный ресурс]. URL: https://zwfw.nmpa.gov.cn/web/taskview/11100000MB0341032Y100207203100001.
21. Мельникова ЕВ, Меркулова ОВ, Меркулов ВА. Мировая практика научного консультирования по вопросам разработки и регистрации инновационных препаратов. БИОпрепараты. Профилактика, диагностика, лечение. 2021; 21 (3): 167–177.
22. FDA. Best Practices for Communication Between IND Sponsors and FDA During Drug Development Guidance for Industry and Review Staff Good Review Practice. U. S. Food and drug administrarion. 2017. Режим доступа: [Электронный ресурс]. URL: https://www.fda.gov/media/94850/download (дата обращения: 05.10.2023).
23. Mandate of the EMA Innovation Task Force (ITF). Режим доступа: [Электронный ресурс]. URL: https://www.ema.europa.eu/en/documents/other/mandate-european-medicines-agency-innovation-task-force-itf_en.pdf (дата обращения: 05.10.2023).
24. EMA. PRIME: priority medicines. Режим доступа: [Электронный ресурс]. URL: https://www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines (дата обращения: 05.10.2023).
25. Режим доступа: [Электронный ресурс]. URL: https://www.ema.europa.eu/en/documents/report/prime-analysis-first-5-years-experience_en.pdf.
26. Guidance on Parallel EMA/HTA body (HTAb) Scientific. Advice for the Interim Period. Режим доступа: [Электронный ресурс].

URL: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guidance-parallel-ema/hta-body-htab-scientific-advice-interim-period_en.pdf (дата обращения: 09.03.2023).
27. FDA. Guidance for Industry Expedited Programs for Serious Conditions. Drugs and Biologics. U. S. Food and drug administrarion 2023. Режим доступа: [Электронный ресурс]. URL: https://www.fda.gov/files/drugs/published/Expedited-Programs-for-Serious-Conditions-Drugs-and-Biologics.pdf (дата обращения: 05.10.2023).
28. EMA. Pre-authorisation guidance. European Medicines Agency. 2018. Режим доступа: [Электронный ресурс]. URL: https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/pre-authorisation-guidance (дата обращения: 11.03.2023).
29. Решение Совета Евразийской экономической комиссии от 03.11.2016 N 78 (ред. от 23.09.2022) "О Правилах регистрации и экспертизы лекарственных средств для медицинского применения", КонсультантПлюс.
30. Resolution of the Collegiate Board. RDC 204/2017 Режим доступа: [Электронный ресурс]. URL: https://antigo.anvisa.gov.br/documents/10181/2718376/RDC_204_2017_.pdf/b2d4ae64-2d91-44e9-ad67-b883c752c094 (дата обращения: 09.03.2023).
31. Resolution of the Collegiate Board. RDC 205/2017. Режим доступа: [Электронный ресурс]. URL: https://bvsms.saude.gov.br/bvs/saudelegis/anvisa/2017/rdc0205_28_12_2017.pdf (дата обращения: 09.03.2023).
32. The draft of the New Drugs and Clinical Trials Rules, 2018, Pub. L. No. D. L.-33004/99 (March 19, 2019).
33. Bishnoi M, Sonker A. Emergency use authorization of medicines: History and ethical dilemma. Perspect Clin Res. 2023;14 (2): 49–55. PubMed PMID: 37325578.
34. Macabeo B, Wilson L, Xuan J, Guo R, Atanasov P, Zheng L, François C, Laramée P. Access to innovative drugs and the National Reimbursement Drug List in China: Changing dynamics and future trends in pricing and reimbursement. J Mark Access Health Policy. 2023; 11 (1): 2218633. PubMed PMID: 37325810.
35. Decree of the State Administration for Market Regulation No. 27. The Provisions for Drug Registration, adopted at the first executive meeting of the State Administration for Market Regulation on January 15, 2020, is hereby promulgated and shall come into force as of July 1, 2020.
36. Keyter A, Banoo S, Salek S, Walker S. The South African Regulatory System: Past, Present, and Future. Front Pharmacol. 2018; 9:1407. PubMed PMID: 30618735.
37. Medicines control council, 2.01_General_information_Jul12_v8_showing_changes.docx (August 2012).
38. Breakthrough Therapy FDA. U. S. Food and drug administrarion. 2018. Режим доступа: [Электронный ресурс]. URL: https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/breakthrough-therapy, (дата обращения: 05.10.20).
39. FDA. SPEVIGO®. U. S. Food and drug administrarion. 2022. Режим доступа: [Электронный ресурс]. URL: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761244s000lbl.pdf (дата обращения: 05.10.2023).
40. Kesselheim AS, Darrow JJ. FDA designations for therapeutics and their impact on drug development and regulatory review outcomes. Clin Pharmacol Ther. 2015; 97 (1): 29–36. PubMed PMID: 25670381.
41. Conditional marketing authorisation Report on ten years of experience at the European Medicines Agency. Режим доступа: [Электронный ресурс]. URL: https://www.ema.europa.eu/en/documents/report/conditional-marketing-authorisation-report-ten-years-experience-european-medicines-agency_en.pdf (дата обращения: 09.03.2023).
42. EMA. Zynteglo. European Medicines Agency. 2019. Режим доступа: [Электронный ресурс]. URL: https://www.ema.europa.eu/en/medicines/human/EPAR/zynteglo (дата обращения: 05.06.2023).
43. ЕАЭС. Кимрая. Режим доступа: [Электронный ресурс]. URL: https://portal.eaeunion.org/sites/commonprocesses/ru-ru/Pages/CardView.aspx?documentId=60dc56f1fb44f1334e36f083&codeId=P.MM.01 (дата обращения: 06.10.2023).
44. Jain P, Chauhan R. India's New Drugs and Clinical Trials Rules: An Industry Perspective. Regulatory Focus. Regulatory Affairs Professionals Society, 2019.
45. Luo X, Du X, Huang L, Guo Q, Lv X, Wang C et al. Evidence of pre-approval clinical trial supporting the granted conditional approval for novel cancer drugs in China between 2015 and 2022. EClinicalMedicine. 2023; 63: 102177. PubMed PMID: 37662522.
46. Sam Bean. What early access opportunities exist for innovative products in China? 2023.
47. China Adopts Revised Drug Administration Law (September 9, 2019).
48. Постановление Правительства РФ от 03.04.2020 N 441 "Об особенностях обращения лекарственных препаратов для медицинского применения, которые предназначены для применения в условиях угрозы возникновения, возникновения и ликвидации чрезвычайной ситуации и для организации оказания медицинской помощи лицам, пострадавшим в результате чрезвычайных ситуаций, предупреждения чрезвычайных ситуаций, профилактики и лечения заболеваний, представляющих опасность для окружающих, заболеваний и поражений, полученных в результате воздействия неблагоприятных химических, биологических, радиационных факторов."КонсультантПлюс.
49. Постановление Правительства РФ от 05.04.2022 N 593 "Об особенностях обращения лекарственных средств для медицинского применения в случае дефектуры или риска возникновения дефектуры лекарственных препаратов в связи с введением в отношении Российской Федерации ограничительных мер экономического характера." КонсультантПлюс.
50. Fast track registration of COVID-19 in Brazil. Режим доступа: [Электронный ресурс]. URL: https://globalregulatorypartners.com/wp-content/uploads/FAST-TRACK-REGISTRATION-OF-COVID-19-VACCINES-IN-BRAZIL.pdf (дата обращения: 20.09.2023).

REAL-WORLD DATA IN LEGAL FRAMEWORK OF THE RUSSIAN FEDERATION

Borzova MA[1], Kalinichenko VV[2], Kolbin AS[3, 4] ✉

[1] Trubor Law Office in Moscow, Moscow, Russia

[2] Department Regulating Circulation of Medicines and Medical Products of the Ministry of Health of the Russian Federation, Moscow, Russia

[3] Pavlov University, Saint-Petersburg, Russia

[4] Saint-Petersburg State University, Saint-Petersburg, Russia

The real-world data (RWD) constitute a modern trend in the healthcare system and in the structure of taking decisions. The trend is being actively developed in the Russian Federation. Ethical aspects of these trials and legal regulation of RWD are, however, still unresolved. In this paper, development of the legal field and national regulation of RWD in Russia is discussed during registration, assessment of healthcare technologies, management of patient registries, and development of clinical recommendations. It is shown that the acting regulatory field of the Russian Federation contains no bans on the use of RWD to support regulatory decisions. Nevertheless, the existing legal laws set limited opportunities for practical application and accounting of RWD by the competent authority. In conclusion, recommendations on further development of RWD legal field in Russia are provided.

Key words: real-world data, regulatory framework

✉ **Correspondence should be addressed:** Aleksey S. Kolbin
Lev Tolstoy Str., 6–8, Saint-Petersburg, 197022, Russia; alex.kolbin@mail.ru

Received: 14.10.2023 **Accepted:** 26.11.2023 **Published online:** 12.12.2023

DOI: 10.24075/medet.2023.031

ДАННЫЕ РЕАЛЬНОЙ КЛИНИЧЕСКОЙ ПРАКТИКИ: ПРАВОВОЕ ПОЛЕ В РФ

М. А. Борзова[1], В. В. Калиниченко[2], А. С. Колбин[3, 4] ✉

[1] Адвокатское бюро города Москвы «Трубор», Москва, Россия

[2] Департамент регулирования обращения лекарственных средств и медицинских изделий Минздрава России, Москва, Россия

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

[4] Санкт-Петербургский государственный университет, Санкт-Петербург, Россия

Данные реальной клинической практики (РКП) — современный международный тренд в системе здравоохранения и в структуре принятия решений. Данное направление активно развивается в Российской Федерации. Однако остаются не решенными этические вопросы проведения данных исследований и правовое регулирование РКП. В статье обсуждаются развитие правового поля национальное регулирование РКП в России: при регистрации, оценке технологий здравоохранения, при введении регистров пациентов, формирование клинических рекомендаций. Показано, что в действующем нормативно-правовом поле Российской Федерации нет прямых запретов на использование данных РКП для поддержки принятия регуляторных решений. Тем не менее, существующие нормы права предусматривают ограниченные возможности для практического применения и учета данных РКП со стороны уполномоченных органов власти. В заключении, даны рекомендации по дальнейшему развитию правового поля РКП в России.

Ключевые слова: данные реальной клинической практики, правовое регулирование

✉ **Для корреспонденции:** Алексей Сергеевич Колбин
ул. Льва Толстого, д. 6–8, г. Санкт-Петербург, 197022, Россия; alex.kolbin@mail.ru

Статья поступила: 14.10.2023 **Статья принята к печати:** 26.11.2023 **Опубликована онлайн:** 12.12.2023

DOI: 10.24075/medet.2023.031

In the recent years, there has been an active public discussion of the modern healthcare system and its place in decision making structure such as real-world data (RWD) and real-world evidence (RWE) [1]. In 2022, Decision of the Council of the Eurasian Economic Commission No. 78 'On introduction of changes into the Rules of registration and expertise of human medicinal products' contains definitions of real-world data (RWD), which relate to a patient's health and/or aid provision and are obtained from different sources. Evidence obtained during analysis of real-world data represent clinical evidence in relation to the use and potential benefit or risk of using a medicine obtained when real-world data were collected and analyzed [2]. Main sources of RWD include electronic health record (EHR) databases and integrated EHR; registries; insurance fund data; patient reported outcomes; outcomes of trials, mainly observational trials, etc. [3–6]. At the same time, ethical issues raised during these trials and regulatory framework of RWD remain globally unsolved.

REGULATION IN THE RUSSIAN FEDERATION

It is shown that the acting regulatory field of the Russian Federation contains no bans on the use of RWD to support regulatory decisions. Nevertheless, the existing legal laws set limited opportunities for practical application and accounting of RWD by the competent authority.

REAL WORLD DATA AND ISSUES OF STATE REGISTRATION OF MEDICINES WITH THE NATIONAL PROCEDURE

In spite of transition of the Russian Federation to registration of medicines as per the rules of the Eurasian Economic Union since January 1, 2021, marketing authorizations issued in accordance with Federal Law as of April 12, 2010 No. 61-FZ 'On circulation of medicines' (hereinafter referred to as Law No. 61-FZ) (which, however, should correspond to the legislation

of the Eurasian Economic Union) are still valid in Russia until December 31, 2025; national registration of separate categories of medicines is still possible within Government Decree of Russia as of April 3, 2020 No. 441 'On peculiarities of circulation of medicines for human use in the face of the threat, occurrence and elimination of an emergency situation, and provision medical aid to persons suffered in the result of emergencies, prevention of emergencies, prevention and treatment of diseases, which constitute a danger to the public, diseases and disorders obtained due to unfavorable chemical, biological and radiation factors' (hereinafter referred to as Decree 441); and Government Decree of Russia as of April 5, 2022 No. 593 'On peculiarities of circulation of human medicinal products in case of a defect or risk of a defect of medicines due to economic restrictions imposed on the Russian Federation' (hereinafter referred to as Decree 593).

Law No. 61-FZ, Decree 441 and Decree 593 contain no terms 'real-world data' or 'real-world evidence', or specialized standards in relation to collection, analysis and use of respective data and evidence. However, Decrees 441 and 593 establish the possibility of accelerated national registration of medicines intended for use in case of emergencies or medicines with a found defect (risk of defect) if the applicant agrees to follow postmarketing measures. The measures can include reported side effects, adverse reactions, serious adverse and unexpected adverse reactions, drug interactions, individual intolerance, other facts and circumstances, which threaten human life or health, or influence the change in the ratio between the expected benefit and possible risk of use of the medicine, detected at all stages of circulation, submitted to the Federal Service for Surveillance in Healthcare, including with the use of web-sites and mobile apps.

Thus, both Decree 441, and Decree 593 indirectly allow using RWD and related RWE as part of compliance with postmarketing surveillance measures by the applicant. It can, however, be used not independently but as part of acting common procedures established by the law. It should also be noted that decision about the possible accelerated state registration of a drug in case of emergency or defect is taken based upon agreement with a commission of experts and (or) ethics council.

RWD AND ASSESSMENT OF HEALTH TECHNOLOGIES

Russian experts repeatedly noted the prospects of using RWD to assess health technologies and compile a list of medicines (such as Essential Drug List), etc. However, irrespective of related offers developed by a professional community and additions to Law No. 61-FZ and Government Decree of Russia as of August 28, 2014 No. 871 'On approval of the Rules for the formation of lists of medicines for human use and minimal assortment of medicines required to render medical aid', direct standards on the possible use of RWD and related RWE have not been included into the legal field yet. According to experts, however, the RWD have been used by pharmacoeconomists de facto for many years to perform clinical and economic analysis and effect on the budget.

Indirect accounting of RWD is set in subpar. (c), par. 5 of the Rules for the formation of a list of medicines, which are purchased in accordance with their trade names (hereinafter referred to as the List) approved by Decree of Government of Russia as of November 28, 2013 No. 1086. In accordance with it, the possible inclusion/exclusion of medicines into/from the List is reviewed based on the outcomes of pharmacovigilance, including data on effectiveness and safety when medicines of different trade names are replaced within the same international non-proprietary name.

At the level of legislation, however, there are examples of successful formation of regional preferential lists of medicines, including the ones taking into account RWD. Thus, in particular, Moscow Government Decree as of December 24, 2021 No. 2180-ПП 'On organization in Moscow of the observational study of effectiveness of some medicines to treat oncological diseases' (along with the 'Order of organization of the observational study of effectiveness of some medicines to treat oncological diseases') shows that citizens with oncological diseases who voluntarily participate in the observational study organized in Moscow obtain compensation for acquisition of administered medicines until December 31, 2023. The observational trial outcomes are examined by 'Moscow Oncological Society' Regional Public Organization to make up suggestions for inclusion of medicines into the system of preferential provision of medicines in Moscow. Respective regional experience can be upscaled in other Russian regions, including the perspective of ethical aspects and better affordability of medical aid.

APPROACHES TO COLLECTION AND USE OF HEALTH-RELATED DATA GENERATED BY MEDICAL DEVICES AND MOBILE APPS

The possibility of distant surveillance over a patient's health using medical devices intended to monitor the state of the body is set in Federal Law as of July 29, 2017 No. 242-FZ 'On introduction of changes into separate legislative acts of the Russian Federation regarding the use of information technologies associated with health protection'. Meanwhile, as per the order of organization and provision of medical aid with the use of telehealth technologies approved by Law of the Ministry of Health of Russia as of November 30, 2017 No. 965н, data can be registered in an automatic mode while using medical devices that can transfer data. The legislation, however, regulates only a small segment of actual doctor-patient relationships. It is reduced to control of patient's health-related values and emergency response when health-related values are deviated from limits. Collection, analysis, generalization and subsequent use of respective data are not regulated by a comprehensive acting legislation.

Nevertheless, on December 9, 2022, Government Decree of Russia No. 2276 'On establishment of experimental legal regime in the sphere of digital innovations and approval of the Program of experimental legal regime in the sphere of digital innovations in a medical activity with the use of collection technologies and treatment of health-related data and diagnoses of citizens regarding the implementation of the initiative of social and economic development of Russia entitled 'Personal medical advisors' was adopted. On December 28, 2022, Government Decree of Russia No. 2469 'On implementation of the pilot project related to remote surveillance over a patient's health using the 'Personal medical advisors' information system (platform)' was adopted. As per the documents, a pilot project regarding remote surveillance over health of patients with arterial hypertension and diabetes mellitus is planned to be implemented until December 31, 2024. Treating physicians can use the data to control vital signs (blood pressure, heart rate, glycemia, at the first stage), which will be recorded by medical devices with the function of remote data transfer. The data are assumed to be transferred to the information system in an impersonal form. Data can be analyzed and treated with the help of AI technologies.

RWD AND PATIENT REGISTRIES

Federal Law as of November 21, 2011 No. 323-FZ 'On fundamentals of health protection of citizens of the Russian Federation' (hereinafter referred to as Law No. 323-FZ) provides for the creation and management of federal registries of patients with separate nosological groups such as Federal registry of HIV-infected persons, Federal registry of persons with TB, Federal registry of persons with life-threatening and chronic progressive rare (orphan) diseases that reduce the life of citizens and incapacitate them; Federal registry of persons with hemophilia, cystic fibrosis, pituitary dwarfism, Gaucher disease, malignant tumors of lymphoid, blood-forming and related tissues, disseminated sclerosis, haemolytic uremic syndrome, systemic-onset juvenile arthritis, types I, II and VI mucopolysaccharidosis, unspecified aplastic anemia, hereditary deficiency of factor II (fibrinogen), VII (labile), X (Stuart-Power) and in persons following transplantation of organs and (or) tissues. Law No. 323-FZ also provides for creation and management of the Federal registry of citizens who are eligible for provision of medicines, medical devices and specialized medical foods at the expense of budgetary allocations from the federal budget and budgets of the regions of the Russian Federation.

Every respective registry is managed in accordance with a special act of Government of the Russian Federation. Moreover, comparison of the registry sections shows that an emphasis is made on the formal collection and analysis of data, subject to the planning of the need in and calculation of the scope of budgetary means to provide patients with medicines, but not on collection, analysis and wide use of real-world clinical data.

Meanwhile, respective registries are managed by the Ministry of Health of Russia and authorized bodies of constituent entities of the Russian Federation, which have to ensure confidentiality of data contained in the federal and regional segment of respective registries, storage and protection of these data in accordance with Federal Law as of July 27, 2006 No. 152-FZ 'On personal data' (hereinafter referred to as Law No. 152-FZ). So, the acting regulations of the Russian Federation state that federal registries can be widely used to analyze real-world data in spite of significant potential use of a respective tool.

As far as ethics and protection of personal data go, the possibility to refer to the federal registries requires significant analysis and elaboration to protect data and basic legal values of patients.

RWD AND ESTABLISHING CLINICAL RECOMMENDATIONS

Compulsory development and review of clinical recommendations are set in Federal Law as of December 25, 2018 No. 489-FZ 'On introduction of changes into article 40 of Federal Law 'On compulsory medical insurance in the Russian Federation' and Federal Law 'On fundamental healthcare principles in the Russian Federation' regarding clinical recommendations. Meanwhile, in accordance with Order of the Ministry of Health of Russia as of February 28, 2019 No. 103н 'On approval of the manner and time of development of clinical recommendations, their review, typical form of clinical recommendations and requirements for their structure, composition and scientific validation of data included into clinical recommendations' (hereinafter referred to as the Order of development and review of CR), clinical recommendations are reviewed at least once every 3 years and no more than once every 6 months.

As per the Order of CR development and review, working groups are formed to develop and review clinical recommendations by medical professional non-commercial organizations. Working groups can include specialists who take part in rendering medical aid in case of a disease or condition (group of diseases or conditions), which demand development of clinical recommendations, scientists, specialists in evidence-based medicine, social workers, representatives of patient organizations, lawyers, representatives of insurance medical organizations, specialists in information technologies and international consultants.

The acting regulations do not exclude the possibility to use the RWD when clinical recommendations are developed if the data are presented and reviewed by respective working groups. Meanwhile, the Order of CR development and review contains generalized methodological approaches to assessment of body of evidence, which make it possible to record RWD when clinical recommendations are formed, and specialized scales assessing the levels of evidence, prevention, treatment and rehabilitation, in particular. However, experts developing clinical recommendations note that it can be complicated to use the mechanisms to assess RWD in practice.

It is also essential to take into account ethical aspects of using RWD when clinical recommendations are formed, especially while mentioning such a young Russian institution as off-label drugs (see part 14.1 of article 37 of Law No. 323-FZ).

EXPERIMENTAL LEGAL REGIME AS A LEGAL BASIS TO COLLECT RWD

RWD collection and analysis require flexible legal regulation, whereas provision of access to medical data and treatment of medical information are significantly complicated by the presence of rigid legal structures, including requirements for protection of personal data and patient confidentiality. To get rid of excessive administrative barriers in the Russian Federation, Federal Law as of July 31, 2020 No. 258-FZ 'On experimental legal regime in the sphere of digital innovations in the Russian Federation' was adopted. It created a legal basis to exempt certain innovative projects from the impact of restrictive legal standards and implement the projects within the so-called 'regulatory sandboxes'.

Moreover, Federal Law as of July 2, 2021 No. 331-FZ 'On introduction of changes into separate legislative acts of the Russian Federation due to the adoption of Federal Law 'On experimental legal regime in the area of digital innovations in the Russian Federation' created a legal basis for non-use of some rigid requirements (regarding treatment of personal data, regarding the possibility of rendering medical aid with telehealth technologies, etc.) for the subjects of the experimental legal regime.

Thus, an economic entity with a status of an operator of an experimental legal regime can obtain additional possibilities to collect and treat anonymized RWD obtained from medical cards of patients.

DISCUSSION OF OBTAINED DATA AND RECOMMENDATIONS

Use of RWD can be an essential tool for regulating authorities while assessing safety and effectiveness of medicines.

Analysis of RWD can provide an idea that a medicine can influence patients in a real life, and not under controlled clinical trials only. This will enable to detect side effects and other factors. which can influence safety and effectiveness. In this

regard, RWD can expand our idea of effectiveness and safety of a medicine.

RWD can also be used for continuous monitoring of medicines after their release to the market. This allows us to identify rare or long-term side effects, which can't be manifested in initial studies, especially if enrollment of patients from different population groups and patients with aggravated history and comorbid conditions was not possible due to objective reasons. Moreover, RWD analysis can also help develop more individualized approaches to treatment taking into account diversity of patients and their needs.

However, there exist some challenges associated with the use of the data, including the need in patient's confidentiality, and potential data distortion due to non-representativeness of the sample. So, approaches to collection and analysis of RWD and especially while taking regulatory decisions should be improved.

Reference

1. Issledovaniya real'noy klinicheskoy praktiki. Obnovlonnyye rekomendatsii 2023 goda. Pod obshchey redaktsiyey Kolbina AS. M.: Izdatel'stvo OKI. 2023; 222 s. ISBN 978-5-907715-17-2. Russian.
2. Resheniye Soveta YEEK № 78 (red. ot 17.03.2022) «O vnesenii izmeneniy v Pravila registratsii i ekspertizy lekarstvennykh sredstv dlya meditsinskogo primeneniya». Available from URL: https://docs.eaeunion.org/docs/ru-ru/01431480/err_18032022_36. Russian.
3. Ivanov AV. Registry kak osnova dlya sbora dannykh i postroyeniya dokazatel'stv. Real'naya klinicheskaya praktika: dannyye i dokazatel'stva. 2021; 1(1): 10–15. https://doi.org/10.37489/2782-3784-myrwd-3 Russian.
4. Mukhina SM, Orlova Ye V. Iskhody, soobshchayemyye patsiyentami: obzor napravleniy primeneniya. Real'naya klinicheskaya praktika: dannyye i dokazatel'stva. 2022; 2(2): 1–7. https://doi.org/10.37489/2782-3784-myrwd-12 Russian.
5. Gusev AV, Zingerman BV, Tyufilin DS, Zinchenko VV. Elektronnyye meditsinskiye karty kak istochnik dannykh real'noy klinicheskoy praktiki. Real'naya klinicheskaya praktika: dannyye i dokazatel'stva. 2022; 2(2): 8–20. https://doi.org/10.37489/2782-3784-myrwd-13
6. Yeremenko YeO, Baranova MI. SENTINEL SYSTEM — elektronnaya sistema dlya sbora dannykh real'noy klinicheskoy praktiki. Real'naya klinicheskaya praktika: dannyye i dokazatel'stva. 2022; 2(2): 32–40. https://doi.org/10.37489/2782-3784-myrwd-15 Russian.

Литература

1. Исследования реальной клинической практики. Обновленные рекомендации 2023 года. Под общей редакцией Колбина А. С. М.: Издательство ОКИ. 2023; 222 с. ISBN 978-5-907715-17-2.
2. Решение Совета ЕЭК № 78 (ред. от 17.03.2022) «О внесении изменений в Правила регистрации и экспертизы лекарственных средств для медицинского применения». Режим доступа: [Электронный ресурс]. URL: https://docs.eaeunion.org/docs/ru-ru/01431480/err_18032022_36.
3. Иванов А. В. Регистры как основа для сбора данных и построения доказательств. Реальная клиническая практика: данные и доказательства. 2021; 1(1): 10–15. https://doi.org/10.37489/2782-3784-myrwd-3
4. Мухина С. М., Орлова Е. В. Исходы, сообщаемые пациентами: обзор направлений применения. Реальная клиническая практика: данные и доказательства. 2022; 2(2): 1–7. https://doi.org/10.37489/2782-3784-myrwd-12
5. Гусев А. В., Зингерман Б. В., Тюфилин Д. С., Зинченко В. В. Электронные медицинские карты как источник данных реальной клинической практики. Реальная клиническая практика: данные и доказательства. 2022; 2(2): 8–20. https://doi.org/10.37489/2782-3784-myrwd-13
6. Еременко Е. О., Баранова М. И. SENTINEL SYSTEM — электронная система для сбора данных реальной клинической практики. Реальная клиническая практика: данные и доказательства. 2022; 2(2): 32–40. https://doi.org/10.37489/2782-3784-myrwd-15

ON JUSTIFIABILITY OF ANIMAL RESEARCH (BASED ON THE ARTICLE BY CAMERON SHELLEY ENTITLED 'WHY TEST ANIMALS TO TREAT HUMANS? ON THE VALIDITY OF ANIMAL MODELS')

Lugowska HG ✉

Pridnestrovian State University named Taras Shevchenko, Tiraspol, Moldova

The article sums up the pros and cons regarding the animal models selected and critically explored by Cameron Shelley in the article entitled 'Why test animals to treat humans? On the validity of animal models'. Special attention is given to the adaptation of the topic-related English version of this discourse for a Russian-speaking reader. Arguments of supporters and opponents of animal models provided by C. Shelley are reviewed. The issue of the effective use of animals in biomedical research considering the validity criterion is being discussed. The connection between the validity and morality of an animal model suggested by C. Shelley is further elaborated. According to C. Shelley, out of three critical arguments for animal modeling, the pseudoscience argument and the disanalogy argument do not work, as the pressing issues they raise are interpreted by supporters in the wrong way. The predictive validity argument is not sufficient, as the doubts raised about the predictive power of animal models are either not supported or lack clear formulation. C. Shelley states that assessing the validity of an animal model is a complex task, which includes various approaches to determining the extent of model validity as appropriate, and defines the problem as an issue of determining the type of validity and its effect on the assessed morality of an animal model. According to the author, ethical issues come down to pragmatics of validity as a criterion capable of disorientating critics of animal modeling or at least reconciling them with the necessity and inevitability of animal experiments.

Keywords: animal tests, animal model, pseudoscience, analogy/disanalogy, model validity, bioethics

✉ **Correspondence should be addressed:** Helena G. Lugowska
Karl Liebknecht Str., 160/122, Tiraspol, 3300, Moldova; lugowska@spsu.ru

Received: 21.08.2023 **Accepted:** 23.10.2023 **Published online:** 29.12.2023

DOI: 10.24075/medet.2023.026

К ВОПРОСУ ОБ ОБОСНОВАННОСТИ ПРОВЕДЕНИЯ ЭКСПЕРИМЕНТОВ НА ЖИВОТНЫХ (ПО МАТЕРИАЛАМ СТАТЬИ CAMERON SHELLEY «WHY TEST ANIMALS TO TREAT HUMANS? ON THE VALIDITY OF ANIMAL MODELS»)

Е. Г. Луговская ✉

Приднестровский государственный университет им. Т. Г. Шевченко, Тирасполь, Молдова

В статье представлены доводы за и против в вопросе использования животного моделирования, отобранные и критически осмысленные Cameron Shelley в статье «Why test animals to treat humans? On the validity of animal models» («Почему для лечения людей нужны тесты на животных? К вопросу об обоснованности проведения экспериментов на животных»). Специально обозначены проблемы адаптации англоязычного дискурса по данному вопросу для русскоязычного читателя. Дан обзор отобранной C. Shelley аргументации сторонников и противников животных моделей, дискутируется вопрос эффективности использования животных в биомедицинских исследованиях с точки зрения критерия валидности; дополнительно рассматривается предложенное C. Shelley соотношение валидности и этичности животной модели. Из трех основных аргументов критики животного моделирования, по C. Shelley, аргумент к лженауке и аргумент к дисаналогии несостоятельны по причине того, что проблемы, которые они поднимают, несмотря на свою актуальность, интерпретируются сторонниками этой аргументации неправильно, а аргумент к прогностической валидности недостаточен, потому что сомнения, которые он вызывает в отношении предсказательной силы животных моделей, либо еще не подтверждены, либо не четко сформулированы. C. Shelley констатирует, что оценка валидности животной модели является сложной, комплексной задачей, включающей различные подходы к определению степени достоверности моделей в зависимости от ситуации их применения, и формулирует эту проблему как вопрос об определении типа валидности и его влияния на оценку этичности животной модели. Этическую проблематику автор сводит к прагматике результативности как критерия, потенциально способного обезоружить противников животного моделирования или хотя бы примирить их с необходимостью и неизбежностью проведения экспериментов на животных.

Ключевые слова: эксперименты на животных, животная модель, аргументация, псевдонаука, аналогия/дисаналогия, достоверность модели, биоэтика

✉ **Для корреспонденции:** Елена Григорьевна Луговская
ул. Карла Либкнехта, д. 160/122, г. Тирасполь, 3300, Молдова; lugowska@spsu.ru

Статья поступила: 21.08.2023 **Статья принята к печати:** 23.10.2023 **Опубликована онлайн:** 29.12.2023

DOI: 10.24075/medet.2023.026

In 2010, Volume 41 of Studies in History and Philosophy of Biological and Biomedical Sciences released an interesting article by Cameron Shelley, PhD (Philosophy), University of Waterloo, Master of Mathematics (Computer Science), with the headline 'Why test animals to treat humans? On the validity of animal models' [1]. It is interesting how the problem is formulated and to which extent the researcher's conclusions can be taken as all-humanitarian ones instead of being a reflection of Western anthropocentrism and attempts to rationalize it.

Specialist in Computer Science with competence in algorithmization and modeling suggests that the issue of animal experiments, which is uneasy from the ethical point of view, should be analyzed with rational logic. In the headline, a set term 'animal models' is used by the author denoting 'the use of animals as laboratory models'. Taking into account the philosophical nature of speculations within the article, we used the term 'animal experiments' in an attempt to be closer to Russian bioethics. In the abstract, the author explains that the subject under discussion is represented by criticism of animal experiments. It is called *animal modeling* in English i.e. *modeling the course of a human biological process or disease using animals because animals are sufficiently like humans*

in their anatomy, physiology or response to a pathogen, and extrapolation of animal tests to humans [2].

To provide an unbiased proper Russian translation of the term 'modeling', the terms 'experiments' or 'tests' (with 'testing', which can also be used, the negative connotation is mitigated with conceptional content of testing something that was already developed unlike conceptional content of verbal combinations with the terms 'tests' and 'experiments', associated with searching, incompleteness or unsuccessfulness, including unpredictable successfulness, of the performed action) are suggested. In this case, it is impossible to completely exclude the negative connotation arising when the terms are used to denote the actions aimed at a living creature. Thus, it is easy for the Russian mind to replace the object in the expression 'animal experiments' with 'human', whereas in English, 'human modeling' means a kind of psychotherapy. A potential positive or negative attitude to the signified is built into the language. Moreover, the word 'treat' has a positive medical connotation meaning 'cure'[1] and implementing the 'improvement' concept.

In English, which is an analytic language, the term 'animal model' can denote both an animal model proper[2] and the result of modeling process[3]. The conceptual difference in the use of the *animal model* and *animal modeling* by C. Shelley is that 'animal modeling' is the principle of research, whereas 'animal model' means an experimental research method applied to an animal[4] [3]. This is the meaning used in Russian medical literature. The term 'animal (experimental) model' is understood differently.

The rhetorical question in the headline contains addubitation (aporia). The first part consists of a special question. It can be translated relying upon the second part only, which is a reference to how the rhetorical question '*Why test animals to treat humans?*' can be answered.

Interpretation of principal notions and terms used in the reviewed article allows us to understand how the author makes a conclusion stating that ethical assessment of using animals to develop and test the methods of struggling human diseases (*animal modeling*) should be reduced to such a question as *'How justifiable is the principle of animal modeling itself based on extrapolation of animal tests to humans and human tests to animals*?'

1. WHY ANIMAL TESTS ARE REQUIRED TO TREAT HUMANS?

The first paragraph of the article by C. Shelley formulates the problem 'Why to test animals?'. Denoting the problem, the author of the article appeals to the text by Kolata [4] published in the New York Times in 2004. Then using the behavioural despair test (see [5], [6]) as an example, the examination of arguments used when criticising animal modeling can be considered as the purpose of the paper.

2. THE PSEUDOSCIENCE ARGUMENT

The pseudoscience argument is the first critical argument. It is consistent with the point of view of Catalano [7] and Greek & Greek [8, 9], who believe that the scientific theories behind animal modeling do not correspond to Popper's falsification principle.

A known historical episode associated with the research of Louis Pasteur is used to prove the assertion. The author adds an important note here related to how the argument is applied to pseudoscience based on analysis of historical examples of using animal modeling when it is incorrect to apply disadvantages of animal modeling of the XIX century to animal model proper (animal modeling per se).

Subsequently, the author challenges the science-based approach to verification. He relies upon the opinion of Lakatos [10] and believes that practical animal modeling does not correspond to theoretical definition. Thus, the idea of animal modeling falsification, which serves as an additional hypothesis but not a theory, is a rhetorical critical flourish and an attempt to depart from the topic.

The author introduces some assertions the validity of which must be supported by the pseudoscience of animal modeling if additional hypotheses are considered on their own as a general theory of animal biology and its connection with human biology. The first assertion states that *the biology of animals is pseudoscience*. According to the second assertion, *the connection between animal biology and human biology is pseudoscience*. The last argument is reviewed separately as the disanalogy argument.

3. THE DISANALOGY ARGUMENT

Here, the author shifts from the issue of science/non-science of practical animal modeling to the issue of the essence of the experimental research method. The question is as follows: *how hypotheses are related to the verified consequences using animal models?* The answer is obvious: 'similarly', as if the animal model is similar to a human condition, it can replace this condition and provoke the respective reaction within the experiment.

It would seem that everything is logical, and a properly asked question provides an exhaustive answer. However, the author notes that '*the analogies <…> are too weak to support the proper connection between theory and verified consequences*. He also formulates the principal requirement for animal modeling as it should ensure theory verifiability.

An assertion by LaFollette & Shanks [11] about the dependence of animal models on the so-called causal analogue model (CAM) is discussed as an argument for disanalogy.

The author follows LaFollette & Shanks [11] and defines disanalogy as *discordance*, the author stresses its inherent inconsistency, as the model can't have a proper cause-effect relation with the objective in the presence of cause-and-effect differences between them. *Face validity*[5] is the term used to prove that. The term (along with 'predictive validity' and 'construct validity' by Willner [12]) is applied in psychological assessment and psychopharmacology.

---

[1] For example, the English word 'treat' is part of the 'What a treat!' expression, creating an emotionally positive attitude and literally translated as 'Such a pleasure!'

[2] '*…an animal model is a non-human species used in biomedical research…<…> animal models (e.g., mice, rats, zebrafish and others) are sufficiently like humans in their anatomy, physiology or response to a pathogen …*' (National Human Genome Research Institut).

[3] See in the following context: *animal model: spontaneous animal models are those for which a particular disease appears naturally in the animal studied. So dogs, for instance, are the only spontaneous animal model for prostate cancer, an important disease in human health. Overall, animal models have proven valuable in studies of nearly every human condition. — Elaine A. Ostrander, Ph.D., Chief & NIH Distinguished Investigator Cancer Genetics and Comparative Genomics Branch* (the same site).

[4] For instance, models with the use of injection methods and transgenic models in research of Alzheimer's disease.

[5] 'Face validity' can be translated as 'face-confirmed' and related to the determination of external (actual) validity as the connection between normal values and the actual behaviour of recipients determining the experience effect. It means that the rate of animal model validity is determined by the analogy to humans.

4. DISANALOGY REVIEW

The author refers to the paper by Willner [12] stating that even external differences in the behaviour of experimental animals reacting to identical experimental conditions, the functional connection between the nature of behavioural reactions and their reasons will support the validity of the model, which is called *construct validity*[6] by Willner.

C. Shelley believes that it is now possible to reformulate the disanalogy argument: to correspond to the requirement of construct but not external (Actual) validity, an animal model should be functionally similar to the model of a human state.

The author refers to the multiconstraint approach by Holyoak и Thagard [13] and uses it to show that disanalogies that make us doubt the validity of the model corresponding to the requirement of construct validity are far from being unconditional. To prove that, he also refers to the Porsolt Forced-Swim (behavioural despair test[7] [14]) and examines the analogy based on the animal model in detail.

Let's consider the functional nature of the model by breaking the analogy formulation into related components. The compared (human and animal) systems will have the following principle components: the object of exposure (human, animal), exposure tool (medicinal agent), behavioural objective, effect and behavioural pattern (specific achievement of behavioural purpose by the target), which also consists of three components: 1) object behavioural strategies (object and its objective), 2) strategical outcome (object and its result), 3) strategy dependance (object and exposure tool), correlation between the result and strategy dependence denoted with '*because*' casualty marker.

By bringing into correlation the compared system components, we conclude that a laboratory rat (exposure object) tries to escape from the cylinder for a longer time (strategy dependence) as it searches for safety (object behavioural purpose) and was administered antidepressant agents (exposure tool). A person in a depressed state (exposure object) is more persistent (strategy dependence) while achieving objectives. The person hoped for success (object behavioural purpose) and was administered antidepressant agents (exposure tool).

To assess the construct validity of the model, the author deals with the analogy using three criteria assessing analogous theories with the multiconstraint approach (to [13]). The author concludes that the analogy satisfies every criterion and is potent enough. So, the Porsolt [14] test has a potent construct validity.

The author mentions the method of applying an additional component (the functionality of which undermines its basis) to the reviewed analogy. According to Schatzberg [4], the author deals with the challenge which was definitely noted by a thoughtful reader: behavioural pattern with the strategies of object behaviour (object and its objective), strategical outcome (object and its result), and strategy dependance (object and exposure tool) display the discrepancy between the cognitive and non-cognitive things by correlation between the result and objective. It is done when the possible effect of antidepressant medications on the exposed brains is examined.

5. THE PREDICTIVE VALIDITY ARGUMENT

Apart from the issues of animal model validity proper, the author of the article deals with the predictive validity concerning Willner [12] who describes it as predictive model strength about the experimental objective.

5.1. The predictive validity argument with a fixed threshold

The argument is defined as follows: animal models are predictively valid when their correlation with human test outcomes exceeds the fixed value.

The approach assessing modeling effectiveness allows many critics to mention false-positive or false-negative results when the developed medicinal agents helped animals but provided no positive effect while used by humans and vice versa[8] [15, 16].

But even if we assume that an absolutely exact calculation of whether the animal model corresponds to target values is possible, the argument with a fixed threshold adds another requirement: the threshold should be practically substantiated.

5.2. The predictive validity argument with a relative threshold

Instead of using the fixed threshold for animal assessment, the author suggests that a relative threshold of validity sufficient for successful modeling should be used. Then the method can be considered invalid based on its less prognostic validity concerning other methods. It means that animal modeling should provide more exact prognoses as compared to the alternative methods (excisions, human testing, computer modification, *in vitro* experiments, epidemiological testing and advanced visualization technologies [17–19, 11, 8].

We agree with the author that though in some cases the use of alternative methods assessing the potential effectiveness of treatment really has a greater predictive strength, it does not mean that animal models are not predictively invalid. If a certain animal model displays less exact outcomes as compared to the alternative one, it is necessary to update the model instead of abandoning it as an ineffective one.

The subsequent author's arguments are aimed at underlining the positive aspects of animal modeling as a sufficiently flexible and potent prognostic method without undermining the significance of alternative approaches to biomedical research.

[6] In specialized literature, *'construct validity'* is considered a specific case of operational validity, which, in turn, is a specific case of the above-mentioned external validity. It displays how adequate is the method of interpretation of experimental data at the core of theory which forms the basis of any model. In biomedical literature, it is a value that justifies the selection of an animal model to achieve the set objective. Animal models react to the experiment with stimulating agents having a stereotyped behavior. It is about the *rearing behavior* for rats and the *scratching behavior* for primates.

[7] According to the experiment, experimental mice who were administered antidepressants continued climbing perfectly smooth cylinder walls and trying to save themselves for a longer time until they stopped moving and changed to passive navigation mode, i.e. lost their hope for success as compared to normal mice given no treatment. The analogy is that a human facing depression will have a greater hope for success if medicinal products are provided. — *L E.*

[8] The case by Barnard Kaufman is provided below as an example. Milrinone obtained through modeling was intended for cardiac support and increased life expectancy in rats with artificially developed heart failure, but actually decreased life expectancy in humans with severe chronic cardiac failure. It is difficult to provide an opposite example because negative modeling results do not mean that the tests will go forward on humans. So, the author uses proof in the first approximation instead of a direct actual one. He cites Florey, who assessed antibiotic penicillin effectiveness on various animal models, including mice and guinea pigs, using different exposure objects for modeling. Thus, therapeutic antibiotic properties of penicillin that provided a positive effect on mice models (but not guinea pigs ones) were supported.

6. ANIMAL MODELS AND KINDS OF ANIMALS

Having examined the arguments of the critics, the author defines the term and formulates two principal approaches to how the term 'animal model' should be defined. He believes that one of them is not correct and, thus, easy to criticize. Though the term 'animal model' is actually available in biomedicine, has a fixed and very narrow meaning and can't be ignored, a literal understanding of the term devalues its significance and undermines the validity of animal modeling outcomes.

7. VALIDITY AND MORALITY OF ANIMAL EXPERIMENTS

In this part, the author states that the validity of animal modeling is an interesting problem. However, discussing the ethics of using animals in medical experiments results in greater attention to the problem. According to this point of view, if the method is invalid, it is wrong to use it to inflict unnecessary suffering on animals (as if it could be less traumatic in case of necessary suffering — *L. H.*).

The ethical issue of animal experiments is replaced with the issue of effectiveness. Previous arguments can be summarized as a determination of whether the animals can be used in biomedical practice considering the rate of experimental success. Now the author believes that not all experiments make animals suffer. Some of them could even bring 'happiness' similar to a human model.

The argument is not devoid of logic. However, the author acts as a hostage to a narrower understanding of the animal model: an experimental animal goes through a special preparation. The fact is not taken into account by the author. Stressing that the experiment can give pleasure and that its outcomes can be useful for the models, the author considers the exposure object only to the extent that its operating within the experiment is essential. Complex examination of the exposure object should include preparation of the object for the exposure. No counterargument provided by the author is useful at any stage yet.

8. VALIDITY AND THE PRECAUTIONARY PRINCIPLE

By failing to refute the arguments of animal modeling critics even by reducing the ethical problem to the issue of validity, the author of the article approaches the issue from a different angle. He suggests that there is no need to accept that animal models are invalid and, thus, not ethical. Instead, it is offered to indicate the indeterminability of their validity and consider the indefinite validity as unacceptable relying upon the precautionary principle. This is how the model validity can be supported. The author refers to the article by O'Riordan & Cameron [20] and concludes that the permissible principle can be applied to the extent it is known that animal modeling is not unacceptable on the grounds of the preventive argument [20].

9. CONLUSIONS

The author concluded that every type of the discussed arguments suggested by critics of animal experiments is aimed to establish the general invalidity of using the method of animal modeling. However, the inconsistency of the arguments can't influence the justifiability of animal research in the aggregate, as the validity of an animal model as a method is still not estimated. This makes its sound criticism difficult.

FINAL REPORT

The article by C. Shelley is a logical and well-substantiated attempt to reduce the critical statements about the unacceptability of animal experiments to the issue of whether it is justifiable to use animals in biomedical practice.

It should be noted that the causality and definition of objectives of some arguments provided by the author are not always transparent. This can be due to the language specifics. In the Russian text, differentiation between a narrow and wide meaning of the term 'animal model' is not only context-dependent but also depends on the use of two various terms such as 'animal model' and 'model of an animal'. At the same time, in some English contexts it is possible to use the 'animal model' and 'model of an animal' as synonyms. It can be generally correlated with the Russian comprehension of an animal model as a tool, instrument and approach to experimental research as the process and principle. However, the pragmatics of considering an animal as an exposure object, which is obligatory for English, is lost when the text is translated into Russian.

Moreover, the Russian terms 'animal model', 'model of an animal' and 'animal modeling' relate to a special scientific discourse only. This makes them sound unbiased and abstract. That is why it is easy to accept the author's arguments about the need to discuss the validity of experiments before the issues of ethics and morality. In the non-specialized discourse, the term 'animal experiments' is most commonly used to cover the issues of biomedical research. Its neutrality is far from being obvious and results in negative connotations. The last makes us look at the issue highlighted by the author from another aspect. The issues of whether experiments on living creatures without their voluntary consent (or even with such consent) are acceptable have been put at the forefront. This is how a constructive discussion turns into an expressive one. From this point of view, the arguments of C. Shelley [1] are useful and interesting not only for those who are involved in biomedical research but also for any civilized person who takes it as a point of view on the issues of bioethics.

References

1. Shelley C. Why test animals to treat humans? On the validity of animal models. Studies in History and Philosophy of Biological and Biomedical Sciences. 2010 Sep; 41(3): 292–9. DOI: 10.1016/j.shpsc.2010.07.002.
2. Animal Model National Human Genome Research Institute. Home. About Genomics Educational Resources. Talking Glossary of Genomic and Genetic Terms. Animal Model Available from URL: https://www.genome.gov/
3. Chin J. Selecting a mouse model of Alzheimer's disease. Methods Mol Biol. 2011; 670: 169–189.
4. Kolata, G. (2004). Of mice and men: Why test animals to cure human depression? New York Times, 28 March. Available from URL: http://www.nytimes.com/2004/03/28/weekinreview /28kola.html.
5. Garibova TL, Krayneva VA, Voronina TA. Povedencheskiye eksperimental'nyye modeli depressii. Farmakokinetika i farmakodinamika. 2017; 3: 14–19. Russian.
6. Yauzina NA, Komleva YuK, Salmina AB, Petrova MM, Morozova GA, Malinovskaya NA, Gertsog GYe. Sovremennyye eksperimental'nyye modeli depressii. Bioiyeditsina. 2013; 1 (1): 61–71. Russian.
7. Catalano GD. Animals in the research laboratory: Science or pseudoscience? Between the species. 1990; 6 (1): 17–21.
8. Greek CR, Greek JS. Sacred cows and golden geese: The human cost of experiments on animals. New York: Continuum. 2000; 227–251.
9. Greek CR, Greek JS. Specious science. How genetics and evolution reveal why medical research on animals harms humans. New York: Continuum. 2002; 288 p.

10. Lakatos I. The methodology of scientific research programmes. Philosophical Papers, 1. Cambridge: Cambridge University Press. 1978; 237–239.
11. LaFollette H, Shanks N. Brute science. Dilemmas of animal experimentation. London: Routledge. 1996; 286 p.
12. Willner P. Methods for assessing the validity of animal models of human psychopathology. In A. A. Boulton, G. B. Baker, & M. T. Martin-Iverson (Eds.), Animal models in psychiatry. Clifton, NJ: Humana Press. 1991; 1–23.
13. Holyoak KJ, Thagard P. Mental leaps: Analogy in creative thought. Cambridge, MA: MIT Press.1995; 320 p.
14. Porsolt RD, Bertin A, Jalfre M. Behavioral despair in mice. A primary screening test for antidepressants. Archives internationales de pharmacodynamie et de therapie. 1977; 9 (2): 327–336.
15. Shelley C. (2002b). The analogy theory of disanalogy: When conclusions collide. Metaphor and Symbol. 2002;17 (2): 81–98.
16. Barnard N, Kaufman SR. (1997). Animal research is wasteful and misleading. Scientific American. 1997; 276(2): 80–82.
17. Fox MA. The case for animal experimentation. Los Angeles: University Of California Press. 1986; 278 p.
18. Salem H. (Ed.). Animal test alternatives: Refinement, reduction, replacement. New York: M. Dekker. 1995; 349 p.
19. Langley CK, Aziz Q, Boutra C, Gordon N, Hawkins P, Jones A, et al. Volunteer studies in pain research — opportunities and challenges to replace animal experiments: The report and recommendations of a Focus on Alternatives Workshop. NeuroImage. 2008; 42(2): 467–473.
20. O'Riordan T, Cameron J. Interpreting the precautionary principle. London: Earthscan. 1994; 316 p.

Литература

1. Shelley C. Why test animals to treat humans? On the validity of animal models. Studies in History and Philosophy of Biological and Biomedical Sciences. 2010 Sep; 41 (3): 292–9. DOI: 10.1016/j.shpsc.2010.07.002.
2. Animal Model National Human Genome Research Institute. Home. About Genomics Educational Resources. Talking Glossary of Genomic and Genetic Terms. Animal Model Available from URL: https://www.genome.gov/
3. Chin J. Selecting a mouse model of Alzheimer's disease. Methods Mol Biol. 2011; 670: 169–189.
4. Kolata G. (2004). Of mice and men: Why test animals to cure human depression? New York Times, 28 March. Available from URL: http://www.nytimes.com/2004/03/28/weekinreview/28kola.html.
5. Гарибова Т. Л., Крайнева В. А., Воронина Т. А. Поведенческие экспериментальные модели депрессии. Фармакокинетика и фармакодинамика. 2017; 3: 14–19.
6. Яузина Н. А., Комлева Ю. К., Салмина А. Б., Петрова М. М., Морозова Г. А., Малиновская Н. А., Герцог Г. Е. Современные экспериментальные модели депрессии. Биомедицина. 2013; 1 (1): 61–71.
7. Catalano GD. Animals in the research laboratory: Science or pseudoscience? Between the species. 1990; 6 (1): 17–21.
8. Greek CR, Greek JS. Sacred cows and golden geese: The human cost of experiments on animals. New York: Continuum, 2000; 227–251.
9. Greek CR, Greek JS. Specious science. How genetics and evolution reveal why medical research on animals harms humans. New York: Continuum. 2002; 288 p.
10. Lakatos I. The methodology of scientific research programmes. Philosophical Papers, 1. Cambridge: Cambridge University Press. 1978; 237–239.
11. LaFollette H, Shanks N. Brute science. Dilemmas of animal experimentation. London: Routledge. 1996; 286 p.
12. Willner P. Methods for assessing the validity of animal models of human psychopathology. In A. A. Boulton, G. B. Baker, & M. T. Martin-Iverson (Eds.), Animal models in psychiatry. Clifton, NJ: Humana Press. 1991; 1–23.
13. Holyoak KJ, Thagard P. Mental leaps: Analogy in creative thought. Cambridge, MA: MIT Press. 1995; 320 p.
14. Porsolt RD, Bertin A, Jalfre M. Behavioral despair in mice. A primary screening test for antidepressants. Archives internationales de pharmacodynamie et de therapie. 1977; 9(2): 327–336.
15. Shelley C. (2002b). The analogy theory of disanalogy: When conclusions collide. Metaphor and Symbol. 2002;17 (2): 81–98.
16. Barnard N, Kaufman SR. (1997). Animal research is wasteful and misleading. Scientific American. 1997; 276 (2): 80–82.
17. Fox MA. The case for animal experimentation. Los Angeles: University Of California Press. 1986; 278 p.
18. Salem H. (Ed.). Animal test alternatives: Refinement, reduction, replacement. New York: M. Dekker. 1995; 349 p.
19. Langley CK, Aziz Q, Boutra C, Gordon N, Hawkins P, Jones A, et al. Volunteer studies in pain research — opportunities and challenges to replace animal experiments: The report and recommendations of a Focus on Alternatives Workshop. NeuroImage. 2008; 42 (2): 467–473.
20. O'Riordan T, Cameron J. Interpreting the precautionary principle. London: Earthscan. 1994; 316 p.

ANALYSIS OF REQUIREMENTS FOR CONFIDENTIALITY AND EXCHANGE OF DIGITAL HEALTH DATA

Alzubaidi AK ✉

Yelets State University named after Bunin IA, Yelets, Russia

The article provides answers to immediate questions associated with the state regulation of confidentiality of information and exchange of data in the era of digital healthcare. The institute of medical confidentiality which originated in the ancient world is still evolving throughout the development of medical law. In the current era of global digitalization, however, the issues related to data confidentiality have become more relevant than ever. With all the modern technologies and digital health care platforms on the rise, new challenges associated with protection of these patients are emerging. To ensure the reliable protection of patient's personal and medical information, doctors and medical institutions have to meet data security standards. It becomes vital to develop effective strategies and mechanisms to prevent unauthorized access and data leakage due to a larger volume of electronic medical records and digital data exchange. Strict rules and standards regulating collection, storage and transfer of medical data belong to a key aspect in this area. The Russian Federation is making great efforts to create the legislation which could protect the rights of patients and made medical establishments to follow the high standards of confidentiality, and to develop technical aids that provide data encryption and protection against hacker attacks.

Keywords: medical secrecy, law, ethics, data disclosure, protection issues, medicine, patient, expert, digital health care, state control, digital rights, personal data protection, digital security, online state services

✉ **Correspondence should be addressed:** Azkhar K. Alzubaidi
Kommunarov Str., 10A, Yelets, Russia; azhrstar90@gmail.com

Received: 14.10.2023 **Accepted:** 25.11.2023 **Published online:** 05.12.2023

DOI: 10.24075/medet.2023.030

АНАЛИЗ ТРЕБОВАНИЙ К КОНФИДЕНЦИАЛЬНОСТИ И ОБМЕНУ ДАННЫМИ ЦИФРОВОГО ЗДРАВООХРАНЕНИЯ

А. К. Алзубаиди ✉

Елецкий государственный университет им. И. А. Бунина, Елец, Россия

Статья отвечает на насущные вопросы, связанные с государственным регулированием конфиденциальности информации и обмена данных в эпоху цифрового здравоохранения. Институт врачебной тайны, зародившийся в Древнем мире, продолжает эволюционировать на протяжении всего развития медицинского права. Однако в наше время, в эпоху глобальной цифровизации, вопросы, связанные с конфиденциальностью информации, стали более актуальными, чем когда-либо. С развитием современных технологий и цифровых платформ здравоохранения возникают новые вызовы в области защиты данных пациентов. Врачи и медицинские учреждения сталкиваются с необходимостью соблюдения стандартов безопасности данных, чтобы обеспечить надежную защиту личной и медицинской информации пациентов. С увеличением объема электронных медицинских записей и цифровых обменов данными становится жизненно важным разработать эффективные стратегии и механизмы для предотвращения несанкционированного доступа и утечек информации. Одним из ключевых аспектов в этой области является установление строгих нормативов и законов, которые регулируют сбор, хранение и передачу медицинских данных. В Российской Федерации активно работают над созданием законодательства, которое защищало бы права пациентов и обязывало медицинские учреждения соблюдать высокие стандарты конфиденциальности, а также разработать технические средства, которые обеспечивают шифрование данных и защиту от хакерских атак.

Ключевые слова: врачебная тайна, закон, этика, раскрытие данных, вопросы защиты, медицина, пациент, эксперт, цифровое здравоохранение, государственный контроль, цифровые права, защита персональных данных, информационная безопасность, электронные госуслуги

✉ **Для корреспонденции:** Азхар Кхудхаир Алзубаиди
ул. Коммунаров, д. 10А, г. Елец, Россия; azhrstar90@gmail.com

Статья поступила: 14.10.2023 **Статья принята к печати:** 25.11.2023 **Опубликована онлайн:** 05.12.2023

DOI: 10.24075/medet.2023.030

At present, digital medical services, which can analyze survey results based on extensive data, have seen rapid growth. So, the issue of medical secrecy and data confidentiality remains highly relevant.

On the one hand, medical secrecy is protected by the state through restrictions and defense mechanisms. On the other hand, the issue is influenced by the ethical part. According to Aleksandra Dronova, State Secretary and Deputy Minister of Health of the Russian Federation, it is regulated by special standards of the medical law. 'Now, when information technologies are being developed, it is essential to ensure medical confidentiality during treatment and protection of data collected from patients', says the expert. Data processing is associated with the risks of its disclosure. Thus, the issue of reliable protection has reached a new level [1].

As per Federal Law as of 21 November 2011 No. 323-FZ 'On fundamental health care principles in the Russian Federation' [2], medical secrecy involves various data including the fact of seeking medical aid by a citizen, condition of health, diagnosis and data obtained during a medical survey and treatment [3]. The law strictly prohibits the disclosure of the data to persons who have acquired them, except as required by law [4].

First, in the presence of written consent of the citizen (authorized representative), information classified as medical secrecy can be transferred to other citizens and qualified persons to conduct a medical survey, treatment and associated procedures [5].

Second, in the absence of written consent, the following cases are allowed (part 4, art. 13, Law No. 323-FZ) [2]:

– to perform a medical survey and treatment of a citizen who is unable to express own will because of his/her condition;

- at risk of spreading infectious diseases, mass poisoning and destructions;
- at the request of state bodies only in cases specified by law, for instance, at the request of inquiry, investigation agencies, or court in connection with an investigation or trial;
- to control whether persons recognized as suffering from drug addiction discharge the duties imposed on them by court;
- when medical aid is provided to the minor;
- to inform the law enforcement agencies of certain cases, such as admission to the hospital of a person who most likely suffered as a result of unlawful actions;
- to have a military medical examination;
- to investigate an industrial accident and a professional disease;
- when medical organizations exchange data;
- to exercise accounting and monitoring within the system of compulsory social insurance;
- to control the quality and safety of a medical activity.

The strict limitations are designed for proper protection of medical secrecy and confidentiality of patients in the Russian Federation. The term 'medical secrecy' does not encompass the full range of individuals who should maintain the secrecy; it refers not to doctors only but to the entire personnel of the medical institution where the patient is admitted and any people who obtained access to the data (for instance, pharmacists or lawyers). The medical secrecy includes not only medical data about the patient's health but also other data such as the patient's location, the fact of seeking medical aid, hospitalization, surveys, etc. [6, 7]

It is stressed in the concept that anybody who has access to medical information of the patients should ensure medical confidentiality, and that by doing so, they maintain patient trust in the medical system.

The legislation of the Russian Federation, namely the Federal Law 'On fundamental health care principles in the Russian Federation' as of 22.07.93 No. 5488-1 (Resolution No. 5488-1) states that citizens have the right to keep it confidential that they referred to medical aid, along with other data submitted by them while asking for medical aid. The rights include a requirement for informed and voluntary consent to medical intervention and a right to refuse from it. The rules and standards of handling medical data are also regulated by the Ethical Code of a Russian Physician (Code, 1994) [8].

As per article 30 entitled 'The Patient's Rights' of the law about fundamental principles, a patient who refers for a medical aid has a right to keep the following information confidential: fact of seeking medical aid, condition of health, diagnosis and other data obtained during examination and treatment as per article 61 hereof. The patient can also select who can obtain access to his/her health-related data (par. 6.9 of article 30) [8].

According to article 31 'Citizens' rights to health information', the data contained within the citizen's medical documents constitutes medical secrecy and can be disclosed without a citizen's consent only in cases set in article 61 hereof. It also guarantees the right of everyone to obtain health-related data in any convenient form including data about the survey results, the presence of a disease, prognosis, methods of treatment, related risks, possible interventions and their consequences, and treatment outcomes [8].

According to article 61 'Medical secrecy', data confirming that medical assistance was sought, information about a citizen's health, diagnosis and other data obtained during an examination and therapy are considered as medical secrecy [8].

The right of citizens for confidentiality of transferred data while obtaining medical assistance and other information constituting medical secrecy entails responsibility of medical workers and other persons for disclosure of data. The responsibility can include administrative, disciplinary or criminal measures in accordance with the legislation of the Russian Federation and republics within the Russian Federation.

Analyzing the regulation of the legal status of medical secrecy, the head of the department of social legislation of the Institute of Legislation and Comparative Law affiliated to the Government of the Russian Federation Natalia Putilo has noted a growing tendency to exclude something belonging to medical secrecy. Thus, the previous edition of the Legislation of the Russian Federation on the Protection of the Health of Citizens (approved by the Supreme Court of Russia as of 22 July 1993 No. 5487-1, which is no longer in effect) had five positions related to the exclusions of medical secrecy disclosure, whereas the previous and current editions of the current law had 10 and 14 positions respectively. It should be noted that according to the decisions taken by the Constitutional Court, the Russian legislation is imperfect as far as medical secrecy goes. Additional grounds have to be established in relation to disclosure of medical secrecy to relatives of deceased patients in certain cases. According to the expert, the respective legislation is under development now. It means that there is a growing number of exclusions in relation to medical secrecy disclosure[2].

The issue about the legislative regulation of telehealth services deserves separate discussion [2]. Telehealth technologies represent the means of distant interaction between medical professionals and patients, identification of participants and records of medical consultations and observations. In the legal society, there exist two opposite opinions about the subsequent regulation of telehealth technologies. Some experts believe that the existing regulation is not sufficient and needs to be more rigid and detailed. Others believe that the current standards are elaborated enough and that excessive regulation prevents novel information technologies from development[9].

In the light of medical sector digitalization, numerous processes of data treatment have gone to electronic format. Increased information puts more responsibility on its safety. Thus, information safety in medicine requires to observe three principles: integrity, accessibility and confidentiality. It is necessary to protect not just information but also the infrastructure used to process the data. Moreover, the medical sphere is a part of critical informational structure; the subjects of the sphere have to protect the data and correspond to safety requirements [1].

Medical institutions have numerous personal data belonging to employees and patients. Many of the data represent medical secrecy [10, 11]. Due to that, their vulnerability to various cyber-threats, either of which represents unique challenges and risks, is increased even more. Ransomware attacks are of particular concern. Let's consider the WannaCry attack in 2017, which seriously affected the National Health Service (NHS) of Great Britain and showed the vulnerability of medical systems to similar threats [12].

Personal medical information (PMI) is highly valued in the black market. So, data theft also poses significant risks. A good example is the Anthem Data Breach of 2015, when hackers were able to steal 79 million member's records [13].

Phishing attack is another common threat aimed at health care workers. Its goal is to extract confidential information or install malware. This is what happened in 2019 at the University of Washington Medicine when a misconfigured server had resulted in almost million of patient data being exposed online [14].

Internal threats, either intentional or accidental, are also a problem in medicine. The incident in 2018 when a nurse of a New-York hospital Illegally obtained access to patients'

medical records by breaching their confidentiality can serve as an example [15].

A growing use of connected medical devices or Internet of Medical Things (IoMT) brings about new vulnerabilities. For instance, FDA report on pacemaker safety made in 2017 underlines potential IoMT related risks [16].

Supply chain attacks is another vector of cyber-threats when intruders target third-party suppliers associated with medical institutions. In 2020, the security of a large American-based hospital system was breached through a supplier. Millions of patients were affected [17].

DDoS (Distributed Denial of Service) attacks can paralyze IT health care systems as in case of DDoS attack launched in April 2014 on Boston Children's Hospital when the operation of the hospital was seriously disrupted [18].

So, information safety in medicine acquires even more importance. Artificial intelligence (AI) is an important ally here as it offers novel solutions to solidify the security of data and keep them confidential. The ability of AI to rapidly analyze huge amounts of data, detect abnormalities and react to online threats revolutionizes the way data protection is handled. AI-based technologies will reformat the methods used by us to protect and treat the confidential data by ensuring a high safety standard within our interconnected world, starting from predictive threat analysis and ending with complex encryption methods [19, 20]. The AI systems are good at analyzing samples and abnormalities seen in the large sets of data, making them more effective in the field of advanced threat detection than regular software. They can examine normal network behavior and rapidly determine deviations, which can point at a security alert such as unauthorized access or attempts of data exfiltration. Early detection is essentially important to prevent or mitigate the consequences of violation of personal data security [21].

AI can respond to threats faster than humans. As soon as a threat is detected, AI can take actions immediately such as isolation of involved systems, block of suspicious network traffic or activation of other security protocols to prevent subsequent damage. Moreover, AI can conduct a predictive analysis based on historical data, which allows to predict and prevent potential safety threats [22].

AI increases data safety by improving encryption methods. By optimizing encryption, AI makes it difficult for unauthorized users to access confidential data. These AI-based encryption methods are constantly evolving and outpace intuder's attempts to crack the security code [23].

The biometric authentication systems represent another area with a significant contribution from AI. AI improves facial recognition, fingerprint scanning and voice recognition by ensuring a better security access to confidential information as compared to traditional passwords [24].

As far as maintenance of confidentiality during data analysis goes, AI can extract valuable data from big data with simultaneous protection of single data points. Some methods such as differential confidentiality prevent data analysis results from breaching individual confidentiality. Moreover, AI tools are crucial to ensure compliance with data protection laws such as Federal Law No. 152-FZ 'Concerning Personal Data' as they automatically evaluate whether the data handling practices within a company correspond to the required legal standards [25].

AI also improves security information and event management (SIEM) systems by correlating and analyzing security signals originating from various sources. This ensures better understanding of potential security threats. Finally, AI is invaluable while assessing templates indicative of a fraudulent activity in critical sectors such as finances and health care protecting institutions and their clients from potential fraud [26].

CONCLUSION

One of the main system requirements of the system is to ensure the confidentiality of a large amount of data accumulated at medical institutions. Due to low protection of confidential data of the existing medical information systems, there are risks that hackers will attack data systems and use personal data of patients and medical professionals for unacceptable purposes.

AI integration into medical information systems makes analysis and solution of common issues, confidentiality and safety, much more effective. AI is essential to reduce the problems by offering complex solutions, which is impossible to do with traditional methods.

AI algorithms can monitor and detect any unusual actions or potential threats within medical information systems. By analyzing patterns and detecting abnormalities, AI can present an early warning system against hacker attacks, which pose a significant risk due to low protection within the existing medical information systems.

Moreover, AI can reduce load on IT personnel at medical institutions by automating routine tasks such as data backup, encryption and disaster recovery. The automation allows to cut expenses and minimize human errors, which can be costly and harmful in sensitive medical data processing.

Finally, AI can increase the total reliability of medical information systems. Use of AI along with advanced algorithms for threat detection and response can result in a higher safety and security, which is crucial in the processing of sensitive medical information.

References

1. Sazonova M. Vrachebnaya tayna i tsifrovizatsiya: kak zashchitit' informatsiyu o patsiyente. Available from URL: https://www.garant.ru/news/1465292/ (data obrashcheniya: 30.03.2023). Russian.
2. Federal'nyy zakon ot 21 noyabrya 2011 g. № 323-FZ «Ob osnovakh okhrany zdorov'ya grazhdan v Rossiyskoy Federatsii» Available from URL: https://base.garant.ru/12191967/ (data obrashcheniya 31.03.2023). Russian.
3. Ivanov AV, Petrov VS. Osobennosti vrachebnoy tayny v kontekste meditsinskogo prava. Zhurnal meditsinskogo prava. 2016; 2: 35–40. Russian.
4. Smirnov Ye P. Zashchita personal'nykh meditsinskikh dannykh v Rossii. Zhurnal prava i interneta. 2018; 10(1): 45–60. Russian.
5. Petrova LL. Pravovyye aspekty peredachi meditsinskoy informatsii. Zhurnal meditsinskogo prava. 2017; 4: 120–135. Russian.
6. Vasil'yev DI. Raskrytiye meditsinskoy informatsii bez soglasiya patsiyenta: zakonodatel'stvo i praktika. Zhurnal zdravookhraneniya i meditsinskogo prava. 2019; 15(2): 200–210. Russian.
7. Federal'nyy zakon ot 27 iyulya 2006 g. № 152-FZ «O personal'nykh dannykh» Rezhim dostupa: [Elektronnyy resurs] URL: https://base.garant.ru/12148567/ (data obrashcheniya 31.03.2023). Russian.
8. Nazarenko GI, Guliyev YaI, Yermakov DYe. Meditsinkiye Informatsionnyye sistemy: teoriya i praktika. Pod red. G. I. Nazarenko, G. S. Osipova. M.: FIZMATLIT. 2005; 320 s. Russian.
9. Sazonova M. Zdorov'ye i tekhnologii: pravovyye problemy vzaimodeystviya. Available from URL: https://www.garant.ru/article/1453970/ (data obrashcheniya 30.03.2023). Russian.
10. Federal'nyy zakon ot 26 iyulya 2017 g. № 187-FZ «O bezopasnosti kriticheskoy informatsionnoy infrastruktury Rossiyskoy Federatsii

Available from URL: https://base.garant.ru/71730198/ (data obrashcheniya 31.03.2023). Russian.
11. Ivanov A, Petrova M. Povysheniye bezopasnosti dannykh v meditsine s pomoshch'yu resheniy na osnove iskusstvennogo intellekta. Zhurnal meditsinskoy informatiki. 2022; 33(4): 207–219. https://doi.org/10.1080/medinf.2022.207219 Russian.
12. CBS News. Massive ransomware attack hits 74 countries. 2017, May 14.
13. Husted ET, Jaffe M. Big Health Care Data Breaches Like Anthem's Are Common. NPR. 2015, February 6.
14. Clarridge C. Data breach at UW Medicine exposes information of nearly 1 million patients. The Seattle Times. 2019, February 20.
15. United States Department of Health and Human Services. Conduent Community Health Solutions of New York. OCR Breach Portal. 2018.
16. U. S. Food and Drug Administration. Firmware Update to Address Cybersecurity Vulnerabilities Identified in Abbott's (formerly St. Jude Medical's) Implantable Cardiac Pacemakers: FDA Safety Communication. 2017, August 29.
17. Whittaker Z. Millions of Americans' medical images and data are left 'unprotected' online. TechCrunch. 2019, September 18.
18. Heimes J. The 10 Biggest Healthcare Data Breaches of 2020, So Far. HealthITSecurity. 2020, June 24.
19. Ellement JR. At first, a hacker was convicted of RICO charges for using a 'botnet.' Boston Globe. 2018, October 1.
20. Smit Dzh., Dzhonson K. Il i setevaya bezopasnost': obnaruzheniye ugroz s pomoshch'yu mashinnogo obucheniya. Zhurnal kiberbezopasnosti. 2022; 18(2):123–135. https://doi.org/10.1080/12345678.2022.1234567. Russian.
21. Li M., Kim YU. Bystryy otklik i ustraneniye kiberugroz s pomoshch'yu sistem na baze Il. Mezhdunarodnyy zhurnal informatsionnoy bezopasnosti. 2023; 22(1): 67–79. https://doi.org/10.1007/s10207-022-00555-4. Russian.
22. Patel' R, Gupta S. Uluchsheniye metodov shifrovaniya dannykh s pomoshch'yu tekhnik Il. Zhurnal prikladnoy kriptografii. 2022; 9(4): 301–317. https://doi.org/10.1016/j.jappcry.2022.03.001. Russian.
23. Tompson A, Chzhan B. Il v biometricheskoy autentifikatsii: novaya era bezopasnosti. Segodnyashniye biometricheskiye tekhnologii. 2023; (1): 14–22. https://doi.org/10.1016/j.btt.2023.01.003. Russian.
24. Devis Ye, Kumar V. Sokhraneniye konfidentsial'nosti dannykh v epokhu Il. Zhurnal zashchity dannykh i konfidentsial'nosti. 2022; 5(2): 210–225. https://doi.org/10.1016/j.jdpp.2022.04.002. Russian.
25. Grin F, Braun L. Il v sistemakh SIYEM: usileniye upravleniya bezopasnost'yu sobytiy. Zhurnal setevoy bezopasnosti. 2022; 17(3): 134–147. https://doi.org/10.1080/15733021.2022.1189072. Russian.
26. Nguyen KH, Chang Dzh. Obnaruzheniye finansovogo i meditsinskogo moshennichestva s pomoshch'yu Il. Zhurnal upravleniya moshennichestvom. 2022; 11(4): 32–45. https://doi.org/10.1080/jfm.2022.11223344. Russian.

Литература

1. Сазонова М. Врачебная тайна и цифровизация: как защитить информацию о пациенте. Режим доступа: [Электронный ресурс] URL: https://www.garant.ru/news/1465292/ (дата обращения: 30.03.2023).
2. Федеральный закон от 21 ноября 2011 г. № 323-ФЗ «Об основах охраны здоровья граждан в Российской Федерации» Режим доступа: [Электронный ресурс] URL: https://base.garant.ru/12191967/(дата обращения 31.03.2023).
3. Иванов А. В., Петров В. С. Особенности врачебной тайны в контексте медицинского права. Журнал медицинского права. 2016; 2: 35–40.
4. Смирнов Е. П. Защита персональных медицинских данных в России. Журнал права и интернета. 2018; 10(1): 45–60.
5. Петрова Л. Л. Правовые аспекты передачи медицинской информации. Журнал медицинского права. 2017; 4: 120–135.
6. Васильев Д. И. Раскрытие медицинской информации без согласия пациента: законодательство и практика. Журнал здравоохранения и медицинского права. 2019; 15(2): 200–210.
7. Федеральный закон от 27 июля 2006 г. № 152-ФЗ «О персональных данных» Режим доступа: [Электронный ресурс] URL: https://base.garant.ru/12148567/ (дата обращения 31.03.2023).
8. Назаренко Г. И., Гулиев Я. И., Ермаков Д. Е. Медицинкие Информационные системы: теория и практика. Под ред. Г. И. Назаренко, Г. С. Осипова. М.: ФИЗМАТЛИТ. 2005; 320 с.
9. Сазонова М. Здоровье и технологии: правовые проблемы взаимодействия. Режим доступа: [Электронный ресурс] URL: https://www.garant.ru/article/1453970/ (дата обращения 30.03.2023).
10. Федеральный закон от 26 июля 2017 г. № 187-ФЗ «О безопасности критической информационной инфраструктуры Российской Федерации» Режим доступа: [Электронный ресурс] URL: https://base.garant.ru/71730198/ (дата обращения 31.03.2023).
11. Иванов А., Петрова М. Повышение безопасности данных в медицине с помощью решений на основе искусственного интеллекта. Журнал медицинской информатики. 2022; 33(4): 207–219. https://doi.org/10.1080/medinf.2022.207219
12. CBS News. Massive ransomware attack hits 74 countries. 2017, May 14.
13. Husted E. T., Jaffe M. Big Health Care Data Breaches Like Anthem's Are Common. NPR. 2015, February 6.
14. Clarridge C. Data breach at UW Medicine exposes information of nearly 1 million patients. The Seattle Times. 2019, February 20.
15. United States Department of Health and Human Services. Conduent Community Health Solutions of New York. OCR Breach Portal. 2018.
16. U. S. Food and Drug Administration. Firmware Update to Address Cybersecurity Vulnerabilities Identified in Abbott's (formerly St. Jude Medical's) Implantable Cardiac Pacemakers: FDA Safety Communication. 2017, August 29.
17. Whittaker Z. Millions of Americans' medical images and data are left 'unprotected' online. TechCrunch. 2019, September 18.
18. Heimes J. The 10 Biggest Healthcare Data Breaches of 2020, So Far. HealthITSecurity. 2020, June 24.
19. Ellement JR. At first, a hacker was convicted of RICO charges for using a 'botnet.' Boston Globe. 2018, October 1.
20. Смит Дж., Джонсон К. ИИ и сетевая безопасность: обнаружение угроз с помощью машинного обучения. Журнал кибербезопасности. 2022; 18(2):123–135. https://doi.org/10.1080/12345678.2022.1234567.
21. Ли М., Ким Ю. Быстрый отклик и устранение киберугроз с помощью систем на базе ИИ. Международный журнал информационной безопасности. 2023; 22(1): 67–79. https://doi.org/10.1007/s10207-022-00555-4.
22. Патель Р., Гупта С. Улучшение методов шифрования данных с помощью техник ИИ. Журнал прикладной криптографии. 2022; 9(4): 301–317. https://doi.org/10.1016/j.jappcry.2022.03.001.
23. Томпсон А., Чжан Б. ИИ в биометрической аутентификации: новая эра безопасности. Сегодняшние биометрические технологии. 2023; (1): 14–22. https://doi.org/10.1016/j.btt.2023.01.003.
24. Дэвис Е., Кумар В. Сохранение конфиденциальности данных в эпоху ИИ. Журнал защиты данных и конфиденциальности. 2022; 5(2): 210–225. https://doi.org/10.1016/j.jdpp.2022.04.002.
25. Грин Ф., Браун Л. ИИ в системах СИЕМ: усиление управления безопасностью событий. Журнал сетевой безопасности. 2022; 17(3): 134–147. https://doi.org/10.1080/15733021.2022.1189072.
26. Нгуен Х., Чанг Дж. Обнаружение финансового и медицинского мошенничества с помощью ИИ. Журнал управления мошенничеством. 2022; 11(4): 32–45. https://doi.org/10.1080/jfm.2022.11223344.

ETHICAL ISSUES OF PHARMACOGENETICS OF ANTI-RELAPSE THERAPY IN PATIENTS WITH ALCOHOL DEPENDENCE SYNDROME

Lileeva EG[1] ✉,Speshilova SA[1], Zinoveva MA[1,2]

[1] Yaroslavl State Medical University, Yaroslavl, Russia

[2] Yaroslavl Regional Clinical Narcological Hospital, Yaroslavl, Russia

Alcohol currently contributes to 5% of the overall global burden of diseases and injuries. Alcohol consumption results in death and disability at young age. Medicinal products approved for treatment of alcohol dependence syndrome include disulfiram, Naltrexone, Cyanamid and nalmefene. Variability of a patient-to-patient pharmacotherapy therapeutic effect can also be associated with genetic causes. Examination of the system of pharmacogenetic markers in narcology will be used to provide for preliminary prognosis of effectiveness and tolerance of medicinal products during personalized anti-relapse (supporting) therapy to support and prolong remission in patients with alcohol dependence.

Key words: alcohol dependence syndrome, anti-relapse therapy, pharmacogenetic testing

Author contribution: the authors reviewed literature data on pharmacogenetic research in patients with alcohol dependence syndrome. The authors made an equal contribution to the article.

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

Received: 13.10.2023 **Accepted:** 26.11.2023 **Published online:** 18.12.2023

DOI: 10.24075/medet.2023.032

ЭТИЧЕСКИЕ ВОПРОСЫ ФАРМАКОГЕНЕТИКИ ПРОТИВОРЕЦИДИВНОЙ ТЕРАПИИ У ПАЦИЕНТОВ С СИНДРОМОМ ЗАВИСИМОСТИ, ВЫЗВАННЫМ УПОТРЕБЛЕНИЕМ АЛКОГОЛЯ

Е. Г. Лилеева[1] ✉, С. А. Спешилова[1], М. А. Зиновьева[1,2]

[1] Ярославский государственный медицинский университет, Ярославль, Россия

[2] Ярославская областная клиническая наркологическая больница, Ярославль, Россия

В настоящее время алкоголем обусловлено 5% общего глобального бремени болезней и травм во всем мире. Потребление алкоголя приводит к смерти и инвалидности в молодом возрасте. Лекарственные препараты, одобренные для лечения синдрома зависимости от алкоголя, включают дисульфирам, налтрексон, цианамид и налмефен. Вариабельность терапевтического эффекта фармакотерапии от пациента к пациенту может быть также связана с генетическими причинами. Изучение системы фармакогенетических маркеров в наркологии будет использовано для предварительного прогноза эффективности и переносимости препаратов в рамках персонализации противорецидивной (поддерживающей) фармакотерапии для поддержания и продления сроков ремиссии у пациентов с синдромом зависимости, вызванным употреблением алкоголя.

Ключевые слова: синдром зависимости, вызванный употреблением алкоголя, противорецидивная терапия, фармакогенетическое тестирование

Вклад авторов: авторами проведен обзор литературных данных по тематике исследования в области фармакогенетических исследований у пациентов с синдромом зависимости, вызванным употреблением алкоголя. Авторы внесли равный вклад в написание статьи.

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

Статья поступила: 13.10.2023 **Статья принята к печати:** 26.11.2023 **Опубликована онлайн:** 18.12.2023

DOI: 10.24075/medet.2023.032

Alcohol is the most actively used psychoactive substance in the world. Its consumption occupies a special place in the list of leading risk factors of population health. Alcohol dependence is still one of the most essential issues whereas basic social losses in the society are mainly associated with this disease and its prevalence [1].

According to the World Health Organization, harmful use of alcohol results in 3.3 million deaths every year, representing 5.9% of all deaths. Excessive alcohol intake is the reason for over 200 health disturbances associated with diseases and injuries. Almost 25% of all death cases among people aged 20–39 years old are associated with alcohol consumption.

Basic alcohol-associated causes of death include poisoning, liver and heart diseases, cancer and car accidents. About 1.38% of global population suffers from alcohol-related diseases. According to the National Medical Research Center named after Serbsky VP of the Ministry of Health of Russia, 1.3% of Russian population is diagnosed with drug intoxication [2].

High incidence of substance-abuse pathology, disease severity, intensity of medical and social consequences and commonly insignificant effect of a standard complex therapy in patients with psychoactive substance (PAS) dependence syndrome make researchers search for specific markers of various types of disease course attributable to various levels of biological (genetic) risk of its development.

Genetic polymorphism means that different variants of gene structures (polymorphic loci or polymorphisms) within the population constitutes a genetic basis both for individual susceptibility to multifactorial and polygenic diseases of hereditary predisposition and a variety of responses to pharmacological agents, including psychoactive substances [3]. Possible dependence on alcohol due to genetic reasons only is essential for two values:

– prevent dependence on alcohol by assessing the individual genetic risk of the disease;
– therapy and rehabilitation: individual contribution of genetic factors into the pathogenesis of a disease

(genetic radical), assessing the genetic effect on effectiveness of pharmacotherapy and rehabilitation programs.

Stabilization of remission and prevention of recurrences constitute a leading treatment trend of alcoholism. Effectiveness and tolerance of medicinal agents used to treat chemical dependency are associated with polymorphism of genes that determine catabolism of drugs within a body, their binding to specific receptors of neuronal membrane involved in the action of drugs proper and PAS that cause dependence, and with the genes regulating the system of brain remuneration using dopaminergic neurotransmission and the system of endogenic opioid neuropeptides.

It is difficult to detect the genes and gene systems due to he results of association study. They can include genome-wide association studies (GWAS) and candidate-gene association studies (CGAS) constituting the genotype of a disease which produces a significant effect on family burden along with non-specificity and multivariance of disease phenotype. Pharmacological study in narcology is the only way to solve such a complex task and trace a pathogenetic approach to the selection of candidate genes [4, 5].

A schematic task of a pharmacogenetic study suggests to correlate the drug effect or a phenotype ad a genotype. It is a set of genes and their polymorphous variants, which can be contributors of differences in the drug effect. Variability of patient-to-patient pharmacotherapy therapeutic effect can also be associated with genetic causes such as differences in the gene structure of direct and indirect drug targets [6]. To improve therapy effectiveness, three approaches can be used:

1) use of long-acting forms of anti-relapsing drugs;
2) combination with other pharmacological drugs that allow to reduce the symptoms leading to a recurrence;
3) patient stratification based on pharmacotherapy effectiveness taking into account a pharmacogenetic analysis. A genetic panel should include genes controlling the most essential links of DA neuromediation such as SOMT and DBH enzymes, dopamine D2 (DRD2) and D4 (DRD4) receptors, dopamine transporters (DAT1) and genes of opioid receptors (the mu (OPRM1) and kappa (OPRK1) opioid receptor) [6].

Medicinal products approved for treatment of alcohol dependence include disulfiram, naltrexone, cyanamid and nalmefene [7]. Moreover, some products for treatment of alcohol dependence displayed possible effectiveness in clinical studies. The available evidential basis is not sufficient for registration of the products as per the indications. These are some anti-epileptic agents (Topiramate, Pregabalin, Gabapentin) and antidepressants such as serotonin reuptake inhibitors (Sertralin), Baclofen and Ondansetron.

A certain effect of polymorphisms associated with genes of mu-opioid receptors (OPRM1), dopamine D2 (DRD2) and D4 (DRD4) receptors, reverse dopamine transporter (DAT), enzyme of metabolism of catechol-O-methyltransferase catecholamines in the modulation of effective opiate dependence remission stabilization with s/c administration of naltrexone was shown in naltrexone long-acting studies [6]. It was established that irrespective of the type of anti-relapse therapy, a number of polymorphic variants increases the risk of dependence recurrence: allele L (2 repeats with 120 bps), DRD4120bp D4 dopamine receptor, allele C DRD2NcoI D2 dopamine receptor, and 9.9 genotype of DATVNTR40bp dopamine reuptake protein (dopamine transporter). Variants of polymorphism (CC+CT)-(TT)) with a combination of genes (OPRK1-DRD2Ncol) increase the probability of treatment completion. Carriers of the same variants (OPRK1-DRD2Ncol) in the group of naltrexone had a higher probability of treatment program completion. The effect was however reverse in the group of double placeboes, and was not manifested in the group of therapy with naltrexone implant [6].

The purpose of another study was to search for gene OPRM1 polymorphism influencing the response to therapy with peroral naltrexone. Statistically significant differences were found in distribution of patients by genotype within subgroups with good, moderate and bad response to therapy. The most pronounced differences in distribution were detected in relation to two genotypes rs6912029 [G-172T] and rs12205732 [G-1510A] (P = 0,05, Fisher exact test). Thus, the association between OPRM1 G-172T and G-1510A gene polymorphism and response to treatment in case of opioid dependence was shown for the first time. The genotypes were more common among non-responders to naltrexone therapy [8].

In the trial of disulfiram preparations, it was shown that the functional polymorphism of dopamine-beta-hydroxylase gene is associated with an increased risk of adverse effects of therapy with disulfiram [9]. This can be explained by an inhibitory effect of disulfiram on dopamine-beta-hydroxylase of brain neurons.

A study of therapeutic effectiveness and safety of using cyanamide in complex therapy of alcohol dependence performed at the National Scientific Center for Narcology in 2006 as compared with traditional treatment of men aged 25 to 60 years [10] has shown that at the stage of remission the drug displayed good effectiveness. Use of cyanamide allowed to decrease a number of early recurrences significantly and, thus, improve the quality of remission. Remission duration depends on the results of a pharmacogenetic testing. In the study of cyanamide by Krupitsky EM and Kibitova AO, the rs1108580 Bst marker was associated with a greater program retention in the group of disulfiram only (LogRank (Mantel-Cox)=0.053), whereas dopamine receptor type 4 (DRD4 120 bp marker) was associated with the less time to failure in the cyanamide (Log Rank (Mantel-Cox)=0.063) group [11].

In the multi-centered randomized placebo-controlled study, Arias et al (2008) [12] discovered associations between polymorphism of A118G (rs561720) of OPRM1 mu-opiate receptor, polymorphisms of rs2234918 (T921C) and rs678849 gene of delta-opiate receptor (OPRD1) and polymorphism of rs963549 gene of kappa-opiate receptor (OPRK1), on the one hand, and exposure of nalmefene on reduced alcohol consumption.

Antiepileptic agents (topiramate, pregabalin, gabapentin) are second-line therapy medicinal products used to treat patients with the syndrome of dependence due to excessive use of alcohol. A significant number of associations of polymorphisms of various genes with the outcomes of alcoholism therapy with pregabalin was detected during pharmacogenetic studies [13]. 30 polymorphic loci of 19 genes of dopamine, noradrenaline, opioid system, GABA system, glutamate, voltage-dependent calcium channels and neurotrophins were investigated. Pharmacogenetic markers of remission retention included as follows: GG BDNF V66M rs6265 (system of neurotrophins), CC DRD2–141C rs1799732 (system of dopamin), CC GRiK-GluR5 rs2832407 (GABA-glutamate system). The CC DRD2–141C rs1799732 option was a specific predictor of long-term retention within a program, whereas CC GRiK-GluR5 rs2832407 was a specific predictor of successful completion of therapy program. Remission duration (time to recurrence) was associated with GG DRD2 Nco I rs6275 (high risk of fast relapse (dopamine system). On the contrary, LL DRD4 48 bp was a marker of fast relapse low risk (dopamine system) [13, 14].

According to literature, the perspective trends of developing the methods for better effectiveness of remission stabilization in case of alcoholism include a combination of pharmacological agents with various targets of action and therapy personalization based on a pharmacogenetic analysis. Based on the outcomes of genotyping, it is possible to detect patients with high resistance to therapy. Preliminary genotyping allows to improve treatment effectiveness before medicinal preparations are administered and provides for clinically useful standardized individual pharmacological treatment strategies to stabilize alcoholism remission.

References

1. Kozhinova TA. Formation and course of alcoholism in men with various character accentuations according to inpatient examination data. Dissertation for the degree of Doctor of Medical Sciences. M., 2019; 4 s. Russian.
2. Kirzhanova VV, Grigorova NI, Bobkov EN, Kirzhanov VN, Sidoryuk OV. Activities of drug treatment services in the Russian Federation in 2020–2021: Analytical review. 2022; 24 s. Russian.
3. Hart AB, Kranzler HR. Alcohol dependence genetics: lessons learned from genome-wide association studies (GWAS) and post-GWAS analyses. Alcohol Clin Exp Res. 2015; 39 (8)1312–1327. DOI: 10.1111/acer.12792
4. Kibitov AO. Genetic aspects of narcological diseases. Monograph. M., 2021; 312 s. Russian.
5. Hall FS, Drgonova J, Jain S, Uhl GR. Implications of genome wide association studies for addiction: are our a priori assumptions all wrong? Pharmacol Ther. 2013; 140(3): 267–279. DOI: 10.1016/j.pharmthera.2013.07.006.
6. Krupitsky EM, Kibitov AO, Blokhina EA, Verbitskaya EV, Brodyansky VM, Alekseeva NP, Bushara NM, Yaroslavtseva TS, Palatkin VYa, Masalov DV, Burakov AM, Romanova TN, Sulimov GYu, Kosten T, Nielsen D, Zvartau EE, Woody D. Stabilization of remissions in patients with opium addiction Naltrexone implant: pharmacogenetic aspect. Zhurnal nevrologii i psikhiatrii im. S. S. Korsakova. 2015; 115 (4): 14–23. Russian.
7. Suzuki Y, Yokoyama A, Nakano M, Okuyama K, Takahashi H, Tamai H, Maruyama K and Ishii H. Cyanamide-induced liver dysfunction after abstinence in alcoholics: a long-term follow-up study on four cases. Alcoholism: Clinical and Experimental Research. 2000; 24: 100–105.
8. Al-Eitan LN, Jaradat SA, Su SY, Tay GK, Hulse GK. Mu opioid receptor (OPRM1) as a predictor of treatment outcome in opiate-dependent individuals of Arab descent. Pharmgenomics Pers Med. 2012; 5: 99–111. DOI: 10.2147/PGPM.S33351.
9. Mutschler J, Abbruzzese E, Witt SH, Dirican G, Nieratschker V, Frank J, Kiefer F. Functional poly-morphism of the dopamine β-hydroxylase gene is associated with increased risk of disulfiram-induced adverse effects in alcohol-dependent patients. Journal of clinical psychopharmacology. 2012; 32 (4): 578–580. DOI:10.1097/JCP.0b013e31825ddbe6.
10. Ivanets NN, Vinnikova MA, Kozyreva AV. Results of clinical and catamnestic comparative study of the drug Cyanamide in the treatment of alcohol dependence. Issues of narcology. 2006; 2: 21–29. Russian.
11. Krupitsky EM, Akhmetova EA, Asadullin AR. Pharmacogenetics of chemical addictions. Review of psychiatry and medical psychology. 2019; (4–1): 12–20. Russian.
12. Arias AJ, Armeli S, Gelernter J, Covault J, Kallio A, Karhuvaara S, Kranzler HR. Effects of opioid receptor gene variation on targeted nalmefene treatment in heavy drinkers. Alcoholism: Clinical and Experimental Research. 2008; 32(7): 1159–1166. DOI:10.1111/j.1530-0277.2008.00735.
13. Krupitsky EM, Rybakova KV, Skurat EP, Mikhailov AD, Neznanov NG. Double-blind, randomized, placebo-controlled study of the effectiveness of the use of pregabalin for the treatment of alcohol dependence syndrome. Voprosy narkologii. 2017; 8: 81–82. Russian.
14. Edenberg HJ, Kranzler HR. The contribution of genetics to addiction therapy approaches. Pharmacol Ther. 2005; 108(1): 86–93.

Литература

1. Кожинова Т. А. Формирование и течение алкоголизма у мужчин с различными акцентуациями характера по данным стационарного обследования: диссертация на соискание ученой степени доктора медицинских наук. М., 2019; 4.
2. Киржанова В. В., Григорова Н. И., Бобков Е. Н., Киржанов В. Н., Сидорюк О. В. Деятельность наркологической службы в Российской Федерации в 2020–2021 годах: Аналитический обзор. 2022; 24 с.
3. Hart AB, Kranzler HR. Alcohol dependence genetics: lessons learned from genome-wide association studies (GWAS) and post-GWAS analyses. Alcohol Clin Exp Res. 2015; 39(8): 1312–1327. DOI: 10.1111/acer.12792.
4. Кибитов А. О. Генетические аспекты наркологических заболеваний. Монография. М., 2021; 312 с.
5. Hall FS, Drgonova J, Jain S, Uhl GR. Implications of genome wide association studies for addiction: are our a priori assumptions all wrong? Pharmacol Ther. 2013; 140 (3): 267–279. DOI: 10.1016/j.pharmthera.2013.07.006.
6. Крупицкий Е. М., Кибитов А. О., Блохина Е. А., Вербицкая Е. В., Бродянский В. М., Алексеева Н. П., Бушара Н. М., Ярославцева Т. С., Палаткин В. Я., Масалов Д. В., Бураков А. М., Романова Т. Н., Сулимов Г. Ю., Костен Т., Ниелсен Д., Звартау Э. Э., Вуди Д. Стабилизация ремиссий у больных опийной наркоманией имплантом налтрексона: фармакогенетический аспект. Журнал неврологии и психиатрии им. С. С. Корсакова. 2015; 115 (4): 14–23.
7. Suzuki Y, Yokoyama A, Nakano M, Okuyama K, Takahashi H, Tamai H, Maruyama K and Ishii H. Cyanamide-induced liver dysfunction after abstinence in alcoholics: a long-term follow-up study on four cases. Alcoholism: Clinical and Experimental Research. 2000; 24: 100–105.
8. Al-Eitan LN, Jaradat SA, Su SY, Tay GK, Hulse GK. Mu opioid receptor (OPRM1) as a predictor of treatment outcome in opiate-dependent individuals of Arab descent. Pharmgenomics Pers Med. 2012; 5: 99–111. DOI: 10.2147/PGPM.S33351.
9. Mutschler J, Abbruzzese E, Witt SH, Dirican G, Nieratschker V, Frank J, Kiefer F. Functional poly-morphism of the dopamine β-hydroxylase gene is associated with increased risk of disulfiram-induced adverse effects in alcohol-dependent patients. Journal of clinical psychopharmacology. 2012; 32(4): 578–580. DOI:10.1097/JCP.0b013e31825ddbe6
10. Иванец Н. Н., Винникова М. А., Козырева А. В. Результаты клинико-катамнестического сравнительного исследования препарата Цианамид в терапии алкогольной зависимости // Вопросы наркологии. 2006; 2: 21–29.
11. Крупицкий Е. М., Ахметова Э. А., Асадуллин А. Р. Фармакогенетика химических зависимостей. Обозрение психиатрии и медицинской психологии. 2019; (4–1): 12–20.
12. Arias AJ, Armeli S, Gelernter J, Covault J, Kallio A, Karhuvaara S, Kranzler HR. Effects of opioid receptor gene variation on targeted nalmefene treatment in heavy drinkers. Alcoholism: Clinical and Experimental Research. 2008; 32(7): 1159–1166. DOI:10.1111/j.1530-0277.2008.00735.
13. Крупицкий Е. М., Рыбакова К. В., Скурат Е. П., Михайлов А. Д., Незнанов Н. Г. Двойное слепое рандомизированное плацебо-контролируемое исследование эффективности применения прегабалина для лечения синдрома зависимости от алкоголя. Вопросы наркологии. 2017; 8: 81–82.
14. Edenberg HJ, Kranzler HR. The contribution of genetics to addiction therapy approaches. Pharmacol Ther. 2005; 108 (1): 86–93.

INTERACTION BETWEEN RISK FACTORS AND INDUCED BLOOD OXIDATION IN PATIENTS WITH STABLE CORONARY ARTERY DISEASE

Shereshneva MV[1] ✉, Ilyin MV[1,2]

[1] Regional Clinical Hospital, Yaroslavl, Russia

[2] Yaroslavl State Medical University, Yaroslavl, Russia

Exposure on key modified risk factors, mainly hypercholesterolemia, arterial hypertension and diabetes mellitus, is an essential component of successful management of patients with coronary artery disease (CAD). As far as the concept of cardiovascular continuum goes, the predisposing behavioral factors that contribute to the development of these abnormal conditions include smoking, hypodynamia and obesity. Oxidative stress is closely associated with atherogenesis at every stage of progression. An open non-randomized prospective study is conducted. An observational group includes 89 patients with stable CAD. Key risk factors of cardiovascular diseases and their correlation with the values of induced blood oxidation were analyzed. Statistically significant ($p < 0.05$) positive correlation between hypercholesteremia and coefficient of oxidative activity ($r = 0.22$), smoking and initial rate of blood oxidation ($r = 0.24$), maximum rate of blood oxidation (r = 0.25), coefficient of oxidative activity ($r = 0.24$), diabetes mellitus and time of the initiation period ($r = 0.25$); negative correlation between smoking and time of the initiation period ($r = –0.4$) were detected. The results obtained show there is a correlation between a lifestyle and oxidative status of patients with stable CAD. Thus, influence on behavioral risk factors is the most important task of management of patients with cardiovascular pathology.

Key words: coronary artery disease, lifestyle, atherosclerosis, oxidative stress

Author contribution: Shereshneva MV — review of up-to-date and foreign literature regarding the examined issue, formulation of the subject study, determining tasks and goals, laboratory research of induced blood oxidation values, mathematical and statistical treatment of data, making conclusions; Ilyin MV — development of research program, formulation of the subject study, determining tasks and goals, mathematical and statistical treatment of data, and making conclusions.

Compliance with ethical standards: the research underwent through an ethical expertise and was approved by the Ethics Committee of the Yaroslavl Medical University of the Ministry of Health of Russia. Prior to inclusion into research, patients received a detailed explanation of tasks and goals, and a voluntary informed consent was obtained.

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

Received: 26.11.2023 **Accepted:** 15.12.2023 **Published online:** 30.12.2023

DOI: 10.24075/medet.2023.033

ВЗАИМОСВЯЗЬ ФАКТОРОВ РИСКА И ПОКАЗАТЕЛЕЙ ИНДУЦИРОВАННОГО ОКИСЛЕНИЯ КРОВИ У БОЛЬНЫХ СТАБИЛЬНОЙ ИШЕМИЧЕСКОЙ БОЛЕЗНЬЮ СЕРДЦА

М. В. Шерешнева[1] ✉, М. В. Ильин[2]

[1] Областная клиническая больница, Ярославль, Россия

[2] Ярославский государственный медицинский университет, Ярославль, Россия

Неотъемлемым компонентом успешного ведения пациентов с ишемической болезнью сердца является воздействие на ключевые модифицируемые факторы риска, прежде всего гиперхолестеринемию, артериальную гипертензию, сахарный диабет. С позиции концепции сердечно-сосудистого континуума, предрасполагающими поведенческими факторами, способствующими развитию данных патологических состояний, являются курение, гиподинамия, ожирение. Окислительный стресс неразрывно связан с процессами атерогенеза на каждом этапе его прогрессирования. Проведено открытое нерандомизированное проспективное исследование. Группа наблюдения представлена 89 больными со стабильной ишемической болезнью сердца. Проанализированы ключевые факторы риска сердечно-сосудистых заболеваний и их взаимосвязь с показателями индуцированного окисления крови. Выявлены статистически значимые ($p < 0,05$) положительные корреляционные связи гиперхолестеринемии и коэффициента окислительной активности ($r = 0,22$), курения и инициальной скорости окисления крови ($r = 0,24$), максимальной скорости окисления крови (r = 0,25), коэффициента окислительной активности ($r = 0,24$), сахарного диабета и времени периода инициации ($r = 0,25$); отрицательная корреляционная связь курения и времени периода инициации ($r = –0,4$). Полученные результаты свидетельствуют в пользу того, что существует связь между образом жизни и оксидативным статусом в популяции пациентов со стабильной ишемической болезнью сердца. Таким образом, одной из важнейших задач в ведении больных с сердечно-сосудистой патологией является влияние на поведенческие факторы риска.

Ключевые слова: ишемическая болезнь сердца, образ жизни, атеросклероз, окислительный стресс

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

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

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

Статья поступила: 26.11.2023 **Статья принята к печати:** 15.12.2023 **Опубликована онлайн:** 30.12.2023

DOI: 10.24075/medet.2023.033

Cardiovascular pathology is still the leading reason for mortality and disability in developed countries including the Russian Federation as almost half of all cases of death occurs due to cardiovascular diseases [1]. In spite of achievements of modern pharmacotherapy, management of patients with high cardiovascular risk is still a non-trivial task in the practice of a clinician. In order for treatment of patients with coronary artery disease to be effective, lifestyle has to be essentially modified.

The well-established term 'risk factor' was introduced into practice during the Framingham Heart Study, the longest epidemiological study in medicine, in 1961. It laid the foundation of modern preventive cardiology and allowed to differentiate between the basic unfavourable factors producing a significant effect on the development of cardiovascular events [2]. The risk factors mainly include arterial hypertension, smoking, diabetes mellitus and hypercholesterolemia. It is important that they are modified.

Atherosclerosis and related oxidative stress represent key pathogenetic links of development and progression of coronary artery disease and cardiovascular events. Biochemical substrate of oxidative stress represents disturbed homeostasis of free radical oxidation and system of antioxidant defence [3–5].

Thus, effectiveness of therapy of cardiovascular diseases is closely associated not only with understanding the pathogenesis of atherosclerosis but also with activities aimed at the correction of modified risk factors [6–8].

PATIENTS AND METHODS

The research was done at the State Budgetary Healthcare Institution of the Yaroslavl region 'Regional Clinical Hospital' (the city of Yaroslavl). The project is included into the program of scientific examination of the Yaroslavl State Medical University and underwent ethical expertise. 89 patients with stable coronary artery disease aged 58.1±8.3 were examined. They included 70 males aged 57.8±8.2 years and 19 females aged 63.9±6.9 years. The diagnosis of CAD was confirmed by outcomes of a clinical research, load tests, coronary angiography data. Drug-induced therapy corresponded to updated clinical recommendations. Key modified factors of cardiovascular risk such as hypercholesteremia in 38 patients, excessive weight or obesity in 75 patients, arterial hypertension in 81 patients, diabetes mellitus in 14 patients and 43 smokers were analyzed (table 1).

The values of induced blood oxidation were assessed using YSI 5300 Biological Oxygen Monitor (Yellow Springs Instrument Company, YSI Inc., USA). Free-radical oxidation of blood components was induced by AAPH water-soluble inducer (2,2-azobis (2-amidino-propane) dihydrochloride).

The oxygen concentration curve was used to determine as follows:

1) rate of blood oxidation (Vox), 10^{-8} mole/L·s;
2) time of initiation period (T), min;
3) initial rate of blood oxidation (Vinit), 10^{-8} mole/L·s;
4) maximum rate of blood oxidation (Vmax), 10^{-8} mole/L·s;
5) ultimate rate of blood oxidation (Vterm), 10^{-8} mole/L·s;
6) coefficient of oxidative activity (OA), %.

Statistical treatment of data was done with STATISTICA 10.0 (StatSoft Inc., USA). Testing for normal distribution of quantitative attributes was done using Kolmogorov-Smirnov's test with Lilliefors and Shapiro-Wilk amendment. To examine the correlation between two attributes, Spearman correlation analysis was used. The study of the type of dependence of an attribute on one or several other attributes was performed based on the logistic regression analysis. The critical value of statistical significance was equal to 5.0%.

RESEARCH OUTCOMES

The results of correlation analysis of induced blood oxidation values and risk factors of cardiovascular complications are presented in table 2.

Among patients with CAD (n = 89), there is a weak but statistically significant (p < 0.05) positive correlation between

Table 1. Characteristics of patients with CAD

Parameters	Number of patients (%)
Total number of patients	89 (100,0)
Men	70 (78,65)
Women	19 (21,35)
age, years (M±SD) men women	58.1±8.3 57.8±8.2 63.9±6.9
Presence of modified risk factors of CAD	
Hypercholesteremia	38 (42.7)
Excessive weight or obesity (BMI ≥ 25 kg/m2)	75 (84.3)
Arterial hypertension	81 (91.0)
Diabetes mellitus	14 (15.7)
Smoking	43 (48.3)

Table 2. Matrix of correlation: risk factors of cardiovascular complications

Value	Vox, 10–8 mol/L•s	Vinit, 10–8 mol/L•s	T, min	Vterm, 10–8 mol/L•s	Vmax, 10–8 mol/L•s	oA, %
BMI	–0.04	0.11	0.01	0.15	0.14	0.01
Smoking	–0.09	**0.24**	**–0.40**	–0.04	**0.25**	**0.24**
AH	–0.2	–0.12	0.13	–0.01	–0.11	–0.18
DM	–0.11	–0.21	**0.25**	–0.02	–0.19	–0.19
Hypercholesteremia	0.01	0.17	–0.20	–0.04	0.11	**0.22**

hypercholesteremia and oxidative activity coefficient (r = 0.22); a weak positive correlation between smoking and initial rate of blood oxidation (r = 0.24), moderate negative correlation with the time of initiation period (r = –0.4), weak positive correlation with the maximum rate of blood oxidation (r = 0.25) and coefficient of oxidative activity (r = 0.24); weak positive correlation between diabetes mellitus and time of initiation period r = 0.25).

DISCUSSION OF RESULTS

Smoking is one of the key behavioral factors that determine the risk of development of unfavorable cardiovascular events. Tobacco smoke contains numerous components, which can result in oxidative damage of cellular structures: reactive oxygen species (ROS) are formed during tobacco incineration and in the process of biotransformation of numerous components forming part of the smoke stream [9]. It is established that smoking promotes decreased activity of the system of antioxidant protection. Smokers undergo through a significantly decreased activity of superoxide dismutase and glutathione peroxidase [10]. Arsenic, lead, cadmium and mercury presenting in the tobacco smoke decrease bioavailability of glutathione [11].

Development and progression of cardiovascular diseases are currently considered within the so-called cardiovascular continuum. The concept offered by Dzau V. and Braunwald E. in 1991 allows to treat a cardiovascular pathology as a continuous abnormal process starting from the effect of risk factors and until cardiac insufficiency and death are developed [12].

CAD substrate includes atherosclerosis which is a cascade of subsequent abnormal changes with oxidation of lipoproteins being an initial stage [13]. Within persisting unfavorable conditions, the basis of which is formed by such risk factors of cardiovascular diseases as arterial hypertension and dyslipidemia, ROS activate pro-inflammatory signaling pathways that promote oxidative modification of lipids and improve their atherogenicity [14, 15].

Hypercholesteremia is one of the most principal factors, which is essential in progression of atherosclerosis [16]. Close interaction between oxidative stress and dyslipidemia values was proven not only among patients with established atherosclerosis but also among those without the established affection of the vascular bed [17–20]. So, one of the most important tasks, which allow to improve patient's quality of life and prognosis is to achieve target values of lipid profile depending on the rate of risk of cardiovascular complications.

Cardiovascular diseases constitute the main reason for death among patients with type 2 diabetes mellitus [21, 22]. Burden of diabetes mellitus is implemented not through progression of atherosclerosis only, but also through a specific complication such as diabetic cardiomyopathy [23]. It is assumed that its development is based on epithelial and mitochondrial dysfunction and glucotoxicity. In the presence of hyperglycemia, advanced glycation endproducts are accumulated within endothelial cells. The process is accompanied by increased production of ROS [24–26].

It is notable that tight glycaemic control is not associated with a decreased rate of cardiovascular events [27, 28], including in medicine of critical conditions [29, 30]. The results show that type 2 diabetes mellitus is a condition, which qualitatively differs from stable hyperglycemia as far as an abnormal effect on the cardiovascular system goes. Prevention of this disease is a pressing issue as well. Modification of lifestyle within the population can significantly reduce the risk of both cardiovascular and overall mortality [31].

CONCLUSIONS

The main therapeutic task within the role of induced blood oxidation in the events of cardiovascular continuum is not so much an indirect effect on atherosclerosis, arterial hypertension or carbohydrate metabolism disorders among patients with stable CAD as it is the effect on primary behavioral risk factors such as smoking, improper feeding, excessive weight and hypodynamia.

Prevention issues are mainly associated with a patient's altered behavior. It depends on many social and mental factors, including the lifestyle of a family and immediate environment. Influence on these factors has a number of objective complications associated with mental and ethical aspects and formation of positive values. The issue of ethical management of real clinical practice needs to be discussed by the medical community in detail and implemented into educational programs for medical professionals.

Reference

1. Boytsov SA, Pogosova NV, Ansheles AA, Badtieva VA, Balakhonova TV, Barbarash OL, et al. Cardiovascular prevention 2022. Russian national guidelines / Russian Journal of Cardiology. 2023; 28(5): 5452. Russian.
2. Kulikov VA. Fremingemskoe issledovanie serdtsa: 65 let izucheniya prichin ateroskleroza. Vestnik VGMU. 2012;2: 16–24. Russian.
3. Poznyak AV, Grechko AV, Orekhova VA, Chegodaev YS, WuWK, Orekhov AN. Oxidative Stress and Antioxidants in Atherosclerosis Development and Treatment. Biology (Basel). 2020; 9(3): 6.
4. Incalza MA, D'Oria R, Natalicchio A, Perrini S, Laviola L, Giorgino F. Oxidative stress and reactive oxygen species in endothelial dysfunction associated with cardiovascular and metabolic diseases. Vascular pharmacology. 2018; 100: 1–19
5. Khosravi M, Poursaleh A, Ghasempour G, Farhad S, Najafi M. The effects of oxidative stress on the development of atherosclerosis. Biological chemistry. 2019; 400(6): 711–732.
6. Hinderliter AL, Smith P, Sherwood A, Blumenthal J. Lifestyle Interventions Reduce the Need for Guideline-Directed Antihypertensive Medication. American journal of hypertension. 2021; 34(10): 1100–1107.
7. Carey RM, Moran AE, Whelton PK. Treatment of Hypertension: A Review. JAMA. 2022; 328(18):1849–1861.
8. Flora GD, Nayak MK. A Brief Review of Cardiovascular Diseases, Associated Risk Factors and Current Treatment Regimes. Current pharmaceutical design. 2019; 25(38): 4063–4084.
9. Goel R, Bitzer ZT, Reilly SM, Foulds J, Muscat J, Elias RJ, et al. Influence of Smoking Puff Parameters and Tobacco Varieties on Free Radicals Yields in Cigarette Mainstream Smoke. Chemical research in toxicology. 2018; 31: 325–331.
10. Ohran H, Evelo CT, Sahin G. Erythrocyte antioxidant defense response against cigarette smoking in humans — the glutathione S-transferase vulnerability. Journal of biochemical and molecular toxicology. 2005; 19: 226–233.
11. Caliri AW, Tommasi S, Besaratinia A. Relationships among smoking, oxidative stress, inflammation, macromolecular damage, and cancer. Mutation research. Reviews in mutation research. 2021; 787: 108365.
12. Podzolkov VI, Osadchiy KK. Serdechno-sosudistiy kontinuum: mogut li ingibitori APF razorvat «porochniy krug»? RMJ. 2008; 17: 1102. Russian.
13. Malekmohammad K, Sewell RDE, Rafieian-Kopaei M. Antioxidants and Atherosclerosis: Mechanistic Aspects. Biomolecules. 2019; 9(8): 301.

14. Bastani A, Rajabi S, Daliran A, Saadat H, Karimi-Busheri F. Oxidant and antioxidant status in coronary artery disease. Biomedical Reports. 2018; 9(4): 327–332.
15. Wolf D, Ley K. Immunity and Inflammation in Atherosclerosis. Circulation research. 2019; 124(2): 315–327.
16. Duggan JP, Peters AS, Trachiotis GD, Antevil JL. Epidemiology of Coronary Artery Disease. The Surgical clinics of North America. 2022; 102(3): 499–516.
17. Belce A, Ozkan BN, Dumlu FS, Sisman BH, Guler EM. Evaluation of Oxidative Stress and Inflammatory Biomarkers Pre and Post-Treatment in New Diagnosed Atherosclerotic Patients. Clinical and experimental hypertension (New York, N.Y.,1993). 2022; 44(4): 320–325.
18. Qin S. LDL and HDL Oxidative Modification and Atherosclerosis. Advances in experimental medicine and biology. 2020; 1276:157–169.
19. Abbasian M, Delvarianzadeh M, Ebrahimi H, Khosravi F, Nourozi P. Relationship between serum levels of oxidative stress and metabolic syndrome components. Diabetes & metabolic syndrome. 2018; 12(4): 497–500.
20. Cabunac P, Karadžov Orlić N, Ardalić D, Banjac G, Ivanišević J, Janać J, et al. Unraveling the role of oxidative stress and lipid status parameters in the onset of preeclampsia. Hypertension in pregnancy. 2021; 40(2): 162–170.
21. Einarson TR, Acs A, Ludwig C, Panton UH. Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007–2017. Cardiovascular diabetology. 2018; 17(1): 83.
22. Ma CX, Ma XN, Guan CH, Li YD, Mauricio D, Fu SB. Cardiovascular disease in type 2 diabetes mellitus: progress toward personalized management. Cardiovascular diabetology. 2022; 21(1): 74.
23. Sorokina AG, Orlova YA. Sovremenniy vzglyad na mekchanizmi razvitiya diabeticheskoy kardiomiopatii i vozmozhnosti ikh korrektsii. RCJ. 2019;11: 142–147. Russian.
24. Knapp M, Tu X, Wu R. Vascular endothelial dysfunction, a major mediator in diabetic cardiomyopathy. Acta pharmacologica Sinica. 2019; 40(1): 1–8.
25. Zhang P, Li T, Wu X, Nice EC, Huang C, Zhang Y. Oxidative stress and diabetes: antioxidative strategies. Frontiers of medicine. 2020; 14(5): 583–600.
26. Robson R, Kundur AR, Singh I. Oxidative stress biomarkers in type 2 diabetes mellitus for assessment of cardiovascular disease risk. Diabetes & metabolic syndrome. 2018; 12(3): 455–462.
27. Santulli G. In type 2 diabetes, intensive glucose control for 5.6 years did not differ from usual care for major CV events at 14 years. Annals of internal medicine. 2019; 171(6): JC31.
28. Reaven PD, Emanuele NV, Wiitala WL, Bahn GD, Reda DJ, McCarren M, et al. Intensive Glucose Control in Patients with Type 2 Diabetes — 15-Year Follow-up. The New England journal of medicine. 2019; 380(23): 2215–2224.
29. Ling Y, Li X, Gao X. Intensive versus conventional glucose control in critically ill patients: a meta-analysis of randomized controlled trials. European journal of internal medicine. 2012; 23(6): 564–574.
30. Yamada T, Shojima N, Noma H, Yamauchi T, Kadowaki T. Glycemic control, mortality, and hypoglycemia in critically ill patients: a systematic review and network meta-analysis of randomized controlled trials. Intensive care medicine. 2017; 43(1): 1–15.
31. Han H, Cao Y, Feng C, Zheng Y, Dhana K, Zhu S, et al. Association of a Healthy Lifestyle With All-Cause and Cause-Specific Mortality Among Individuals With Type 2 Diabetes: A Prospective Study in UK Biobank. Diabetes care. 2022; 45(2): 319–329. https://doi.org/10.2337/dc21-1512.

Литература

1. Бойцов С. А., Погосова Н. В., Аншелес А. А., Бадтиева В. А., Балахонова Т. В., Барбараш О. Л. и соавт. Кардиоваскулярная профилактика 2022. Российские национальные рекомендации. Российский кардиологический журнал. 2023; 28(5): 5452.
2. Куликов В. А. Фремингемское исследование Сердца: 65 лет изучения причин атеросклероза. Вестник ВГМУ. 2012; 2: 16–24.
3. Poznyak AV, Grechko AV, Orekhova VA, Chegodaev YS, WuWK, Orekhov AN. Oxidative Stress and Antioxidants in Atherosclerosis Development and Treatment. Biology (Basel). 2020; 9(3): 6.
4. Incalza MA, D'Oria R, Natalicchio A, Perrini S, Laviola L, Giorgino F. Oxidative stress and reactive oxygen species in endothelial dysfunction associated with cardiovascular and metabolic diseases. Vascular pharmacology. 2018; 100: 1–19
5. Khosravi M, Poursaleh A, Ghasempour G, Farhad S, Najafi M. The effects of oxidative stress on the development of atherosclerosis. Biological chemistry. 2019; 400(6): 711–732.
6. Hinderliter AL, Smith P, Sherwood A, Blumenthal J. Lifestyle Interventions Reduce the Need for Guideline-Directed Antihypertensive Medication. American journal of hypertension. 2021; 34(10): 1100–1107.
7. Carey RM, Moran AE, Whelton PK. Treatment of Hypertension: A Review. JAMA. 2022; 328(18): 1849–1861.
8. Flora GD, Nayak MK. A Brief Review of Cardiovascular Diseases, Associated Risk Factors and Current Treatment Regimes. Current pharmaceutical design. 2019; 25(38): 4063–4084.
9. Goel R, Bitzer ZT, Reilly SM, Foulds J, Muscat J, Elias RJ, et al. Influence of Smoking Puff Parameters and Tobacco Varieties on Free Radicals Yields in Cigarette Mainstream Smoke. Chemical research in toxicology. 2018; 31: 325–331.
10. Ohran H, Evelo CT, Sahin G. Erythrocyte antioxidant defense response against cigarette smoking in humans — the glutathione S-transferase vulnerability. Journal of biochemical and molecular toxicology. 2005; 19: 226–233.
11. Caliri AW, Tommasi S, Besaratinia A. Relationships among smoking, oxidative stress, inflammation, macromolecular damage, and cancer. Mutation research. Reviews in mutation research. 2021; 787: 108365.
12. Подзолков В. И., Осадчий К. К. Сердечно-сосудистый континуум: могут ли ингибиторы АПФ разорвать «порочный круг»? РМЖ. 2008; 17: 1102.
13. Malekmohammad K, Sewell RDE, Rafieian-Kopaei M. Antioxidants and Atherosclerosis: Mechanistic Aspects. Biomolecules. 2019; 9(8): 301.
14. Bastani A, Rajabi S, Daliran A, Saadat H, Karimi-Busheri F. Oxidant and antioxidant status in coronary artery disease. Biomedical Reports. 2018; 9(4): 327–332.
15. Wolf D, Ley K. Immunity and Inflammation in Atherosclerosis. Circulation research. 2019; 124(2): 315–327.
16. Duggan JP, Peters AS, Trachiotis GD, Antevil JL. Epidemiology of Coronary Artery Disease. The Surgical clinics of North America. 2022; 102(3): 499–516.
17. Belce A, Ozkan BN, Dumlu FS, Sisman BH, Guler EM. Evaluation of Oxidative Stress and Inflammatory Biomarkers Pre and Post-Treatment in New Diagnosed Atherosclerotic Patients. Clinical and experimental hypertension (New York, N.Y., 1993). 2022; 44(4): 320–325.
18. Qin S. LDL and HDL Oxidative Modification and Atherosclerosis. Advances in experimental medicine and biology. 2020; 1276: 157–169.
19. Abbasian M, Delvarianzadeh M, Ebrahimi H, Khosravi F, Nourozi P. Relationship between serum levels of oxidative stress and metabolic syndrome components. Diabetes & metabolic syndrome. 2018; 12(4): 497–500.
20. Cabunac P, Karadžov Orlić N, Ardalić D, Banjac G, Ivanišević J, Janać J, et al. Unraveling the role of oxidative stress and lipid status parameters in the onset of preeclampsia. Hypertension in pregnancy. 2021; 40(2): 162–170.
21. Einarson TR, Acs A, Ludwig C, Panton UH. Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007–2017. Cardiovascular diabetology. 2018; 17(1): 83.
22. Ma CX, Ma XN, Guan CH, Li YD, Mauricio D, Fu SB. Cardiovascular disease in type 2 diabetes mellitus: progress toward personalized management. Cardiovascular diabetology. 2022; 21(1): 74.

23. Сорокина А. Г., Орлова Я. А. Современный взгляд на механизмы развития диабетической кардиомиопатии и возможности их коррекции. РКЖ. 2019;11: 142–147.
24. Knapp M, Tu X, Wu R. Vascular endothelial dysfunction, a major mediator in diabetic cardiomyopathy. Acta pharmacologica Sinica. 2019; 40(1): 1–8.
25. Zhang P, Li T, Wu X, Nice EC, Huang C, Zhang Y. Oxidative stress and diabetes: antioxidative strategies. Frontiers of medicine. 2020; 14(5): 583–600.
26. Robson R, Kundur AR, Singh I. Oxidative stress biomarkers in type 2 diabetes mellitus for assessment of cardiovascular disease risk. Diabetes & metabolic syndrome. 2018; 12(3): 455–462.
27. Santulli G. In type 2 diabetes, intensive glucose control for 5.6 years did not differ from usual care for major CV events at 14 years. Annals of internal medicine. 2019; 171(6): JC31.
28. Reaven PD, Emanuele NV, Wiitala WL, Bahn GD, Reda DJ, McCarren M, et al. Intensive Glucose Control in Patients with Type 2 Diabetes — 15-Year Follow-up. The New England journal of medicine. 2019; 380(23): 2215–2224.
29. Ling Y, Li X, Gao X. Intensive versus conventional glucose control in critically ill patients: a meta-analysis of randomized controlled trials. European journal of internal medicine. 2012; 23(6): 564–574.
30. Yamada T, Shojima N, Noma H, Yamauchi T, Kadowaki T. Glycemic control, mortality, and hypoglycemia in critically ill patients: a systematic review and network meta-analysis of randomized controlled trials. Intensive care medicine. 2017; 43(1): 1–15.
31. Han H, Cao Y, Feng C, Zheng Y, Dhana K, Zhu S, et al. Association of a Healthy Lifestyle With All-Cause and Cause-Specific Mortality Among Individuals With Type 2 Diabetes: A Prospective Study in UK Biobank. Diabetes care. 2022; 45(2): 319–329. https://doi.org/10.2337/dc21-1512.

MEDICAL STUDENTS IN CLINICAL TRAINING: ETHICAL ASPECTS

Deeva VA, Guseva EV, Demyanov VS, Isaeva PA, Polushkina MA, Ruck DM, Tihonova AS, Kim TG ✉

Pirogov Russian National Research Medical University, Moscow, Russia

The article is devoted to ethical aspects of bedside training. Education of future specialists in the clinical setting is important to acquire knowledge, skills, professional competencies and to form clinical thinking. Transfer of professional medical experience occurs simultaneous to the development of communication skills which are required to deal with patients, their relatives, colleagues and mentors. It is about comprehension of how the normal standards of medical deontology are implemented in real practice and how important the effective therapeutic alliance is while interacting with the patient. Though bedside training is a long-standing tradition of medical education, the origins of which are associated with the Ancient Greek Healing Practices, it is not always understood and supported by patients and their relatives, and requires students to get more familiar with ethical standards regulating similar education and their behavior within a medical group and institution.

Keywords: bedside training, students in the hospital, bioethics in medical education

Acknowledgements: Aleksander G. Chuchalin for a conference in bioethics and presenting data related to the 'Bioethics Library', Elena G. Grebenschikova for participation in a student's bioethics conference, consultation related to the topic of the article, and manuscript correction.

Author contribution: Deeva VA, Guseva EV, Demyanov VC, Isaeva PA, Polushkina MA, Ruck DM, Tihonova AC, Kim TG — all authors made equal contributions to the preparation of the text.

✉ **Correspondence should be addressed:** Tatiana G. Kim
ul. Ostrovityanova, 1, Moscow, 117321, Russia; tnkim@mail.ru

Received: 31.10.2023 **Accepted:** 12.11.2023 **Published online:** 29.12.2023

DOI: 10.24075/medet.2023.028

СТУДЕНТЫ В КЛИНИКЕ: ЭТИЧЕСКИЕ АСПЕКТЫ

В. А. Деева, Е. В. Гусева, В. С. Демьянов, П. А. Исаева, М. А. Полушкина, Д. М. Рак, А. С. Тихонова, Т. Г. Ким ✉

Российский национальный исследовательский медицинский университет имени Н. И. Пирогова, Москва, Россия

Статья посвящена этическим аспектам проблемы обучения студента у постели больного. Обучение будущих специалистов в клинике играет важную роль для приобретения знаний, навыков, профессиональных компетенций и формирования клинического мышления. Вместе с передачей врачебного опыта происходит развитие коммуникативных навыков, необходимых для общения как с пациентами и их родственниками, так и с коллегами, наставниками, складывается понимание того, как реализуются нормы медицинской деонтологии в реальной практике и какое значение имеет эффективный терапевтический альянс в процессе взаимодействия с больным. Несмотря на то что обучение у постели больного — давняя традиция в медицинском образовании, истоки которой связаны с древнегреческой практикой врачевания, оно не всегда встречает понимание и поддержку среди пациентов и их родственников, требует большего знакомства студентов с этическими нормами, которые регламентируют подобное обучение и их поведение в медицинском коллективе и учреждении.

Ключевые слова: обучение у постели больного, студенты в клинике, биоэтика в медицинском образовании

Благодарности: Александра Григорьевича Чучалина за проведение конференции по биоэтике, предоставление информации «Библиотека по биоэтике», Елену Георгиевну Гребенщикову за участие в студенческой конференции по биоэтике, консультирование по теме статьи, коррекции рукописи.

Вклад авторов: В. А. Деева, Е. В. Гусева, В. С. Демьянов, П. А. Исаева, М. А. Полушкина, Д. М. Рак, А. С. Тихонова, Т. Г. Ким — все авторы внесли равный вклад в подготовку текста.

✉ **Для корреспонденции:** Татьяна Геннадиевна Ким
ул. Островитянова, д. 1, г. Москва, 117321, Россия; tnkim@mail.ru

Статья поступила: 31.10.2023 **Статья принята к печати:** 12.11.2023 **Опубликована онлайн:** 29.12.2023

DOI: 10.24075/medet.2023.028

Hospital-based education of future specialists is important to acquire knowledge, skills and abilities, professional competencies and to form clinical thinking. Transfer of professional medical experience occurs simultaneous to the development of communication skills which are required to deal with relatives, comprehension of how the normal standards of medical deontology are implemented in real practice and how important the effective therapeutic alliance is while interacting with the patient.

Though bedside training is a long-standing tradition of medicine, the origins of which are associated with the Ancient Greek Healing Practices, it is not always understood and supported by patients and their relatives, and requires students to get more familiar with ethical standards regulating similar education and their behavior within a medical group and institution.

The goal of the article is to review ethical aspects of bedside training.

THE HISTORY OF THE PROBLEM

Bedside training of future doctors is associated with the Ancient Greek Healing Practices and medicine of peoples of the ancient and medieval East. However, during the Middle Ages, medicine in Europe was taught through books approved by religious leaders. The situation changed during the Renaissance when Giovanni Battista Montano from the University of Padua began implementing clinical (bedside) teaching claiming that 'teaching

is possible at bedside only'. Nevertheless, it was merely book learning, as in European medical education, the effect of scholasticism persisted for quite a long time.

The key role in the development and implementation of clinical teaching was played by the University of Leiden (the Netherlands) and Boerhaave Hermann who was in charge of the University Hospital. He introduced bedside, or clinical, teaching for medical students. . Boerhaave was a teacher of Nicolaas Bidloo from Amsterdam who was responsible for the formation of higher medical education in Russia. In 1702, Bidloo was invited to Russia and became a personal physician of Tsar Peter I. In 1707, he was the head of the first hospital school in Russia opened in Moscow at the initiative of Peter I [1].

In the beginning of the last century, Veresaev VV in his 'Memoirs of a Physician' paid attention to the challenges of medical education in Russia: 'The knowledge obtained by me at the University constituted the chaotic terrain, which I couldn't navigate and in front of which I stood in utter helplessness. The mere science presented in books and not tested by me in real life cheated on me over and over again; its solid and fixed forms could not accommodate a new life; and I never knew how to make these forms elastic and mobile. I was always wrong in my attempts to predict the further course of the disease and was afraid to show my face to patients' [2]. Discussing the problems of professional medical training in his book, Veresaev VV showed the role of ethics in the development of a future specialist who should not only feel compassion and sympathy to the patient, but also be able to assess himself properly, understand and admit own incompetence and even mistakes. It is not accidental that the writer mentions the book by Pirogov NI 'The Annals of a Surgical Hospital' when the issue of a medical mistake has been raised as a matter of concern. Meanwhile, Veresaev VV noted as follows: 'No matter how sad it is, but we should admit that our science is still free of ethics. What we really have to deal with is specialized corporate medical ethics that regulates the attitude of doctors to the public and their colleagues' [2].

The circumstances described by Veresaev VV did not go through immediate changes. However, the medical community gradually recorded the basic standards of medical ethics within the documents, and ethical codes in particular. The 'Ethical Code for Medical and Pharmaceutical Students' is one of the documents with interesting provisions related to hospital-based education [3].

THE ETHICAL CODE FOR MEDICAL AND PHARMACEUTICAL STUDENTS

Hospital-based education imposes certain obligations upon students. The obligations are associated with compliance with the standards and rules of a medical institution, and communication with teachers and other medical workers. The Ethical Code for Medical and Pharmaceutical Students was developed by members of the Council of Medical and Pharmaceutical Universities of Russia and adopted in 2015 during the IV All-Russian Forum of Medical and Pharmaceutical University Students [4]. The Ethical Code (EC) consists of 5 articles; it is mainly oriented at high morality, medical ethics and deontology, dignity, conscience and distinguished title of a medical worker. In our opinion, the most important provisions of the EC regulating the education of students at a hospital were presented in some articles.

In article 3, they claim that the relations between students, teachers, hospital employees and patients should be based on 'mutual respect and cooperation, tacts and correctness, politeness and mutual aid…'. Any forms of humiliation of honor and dignity, physical and mental personal violence, use of obscene, curse and slang language while talking to patients, senior colleagues and other students are prohibited. Maintaining cleanliness of the hospital is no less essential.

Article 4 regulates the student's appearance. It should correspond to standards and operating conditions of medical institutions. Students should wear clean white lab coats or medical costumes and look professional. Wearing a medical cap and spare shoes is essential as well. Girls should tie their hair back. It should be noted that '*sharp odor cosmetics and perfume, gel manicure, unproper (large) gold/silver ware, fashion jewellery, and high heel shoes are not ethically approved*'.

Article 5 gives us an idea of how to behave and interact with employees of a medical institution. A special attention is given to being polite and displaying mutual respect. Thus, while meeting employees of a University department or a medical institution, a student always greets the persons even if he does not know them personally. It is also necessary to respect a patient's honor and dignity and the right to personal secrecy. Always remember about your patient's relatives and try to understand their feelings.

Thus, it is extremely important that students of clinical hospitals should follow the EC and related rules, as a physician should not only accumulate medical knowledge but also have high moral principles. Nevertheless, patients are not always ready to interact with students who undergo through training.

A HOSPITAL AS A CLINICAL BASE OF THE UNIVERSITY: INTERACTION WITH PATIENTS.

Not all patients are aware of the fact that while being hospitalized, they sign documents stating that a medical institution is a clinical base of the University. Thus, students of the medical university can attend and examine patients freely, and collect the history. Students are commonly rejected by patients who do not agree to be examined (the problem is very pressing in case of a female patient and a male student). But patients are human, too. They can get tired (especially when one patient is visited by many groups of students), feel bad, and be at a loss or sorrow because of their disease. In our opinion, there is a solution to the problem.

1. When patients are hospitalized, the hospital employees should stress that a hospital is a clinical base of the University and that students should stay at wards, collect history and carry out an examination.
2. Students should be presented to the patients as future doctors who possess the necessary knowledge, follow deontology and can keep the medical secret.
3. Students should be explained why working directly with patients is important for them. Theoretical knowledge with no practical experience would prevent them from being good specialists who will treat the patient, friends and relatives.
4. Students should also be able to put themselves into the patient's position: understand the patient's condition, respect the person's personal space, visit patients in small groups without making them feel uncomfortable.

The provisions should be followed even if they are not reflected in the EC for Medical and Pharmaceutical Students.

HOSPITAL AS A CLINICAL BASE FOR PRACTICAL TRAINING: INTERACTION WITH MEDICAL PERSONNEL.

Modern medical education is impossible without visual memorizing and practical experience. You can read a book, articles, scientific research, keep repeating symptoms and syndromes, clinical picture of the disease, but only real bedside experience can promote long-term memorization. It often happens that students may also have difficulties while communicating with hospital personnel. For instance, students don't adhere to the hierarchical order or come to the hospital when they do not feel well without even wearing individual protection means. It can produce a negative effect not only on a student who violated the rules but also on his colleagues. Thus, students can be prohibited to visit patients and stay in wards. What measures can prevent possible educational problems?

1. A teacher should be open to professional communication explaining treatment specifics especially when students feel that the treatment strategy is wrong and when they want their mentor to make the situation clearer; explaining how to communicate with patients and their relatives; explaining the hospital rules, including evident aspects which are missed out such as neat clothing, punctuality, and subordination in dealing with nursing staff. It is important to remember that students, patients and hospital employees are eligible for a kind attitude and respect.
2. Sick students should stay at home and not to expose patients to additional risks. However, a missed class means that a student can't deal with the problem in practice, and examine a patient. The gap should be filled by agreement with a teacher or treating physician, and the possibility will be a significant factor of compliance with sanitary and epidemiological standards. It is also essential that the students should understand that the situation is exceptional and should not trespass upon the attitude of a teacher or treating physician.
3. Teachers who are eager to share their experience in solving moral and psychological problems faced by some students are playing an important role. For instance, severe obstacles for proper examination can include disgust or lack of patience while talking to suspicious or elderly people, which may further make communication difficult as the patient will feel the bad attitude and will doubt whether the treatment was proper, etc.

PROFESSIONALISM IN MEDICINE AND EDUCATIONAL CHALLENGES AT A HOSPITAL

During the last decades, the issues of professionalism in medicine attract the attention of many researchers who advert to ethical aspects of a physician's activity. In this perspective, professionalism can be considered as a physician's preparedness for responsible work such as being integral while performing own duties, displaying high standards towards own knowledge, professional competencies and self-education, and taking into account ethical aspects while performing medical procedures in clinical practice. Academician Petrovsky BV stressed that 'personal responsibility should be based on the constant strive of a physician towards theoretical knowledge and improvement of practical skills, continuous upgrade of professional skills by using the critical analysis of observations, examination of mistakes, learning from the older colleagues and reading literature, and raising ethical and deontological standards' [4].

A professional should be able to listen to a patient, explain the situation clearly and to prove conclusively the need for certain medical appointments. It is essential to understand the specifics of various areas of medicine. The fact is stressed by academician Chuchalin AG in his 'Interview with a physician' by suggesting the bases for development of the individual diagnostic algorithm for every doctor. Academician Chuchalin AG emphasizes the importance of bioethics for education of a future medical specialist: 'A modern doctor is, first of all, a well-educated, highly competent and thinking specialist with high moral standards'. What should a physician's mission be like in Russia? A physician should protect health, display deep respect for human dignity, personality and life. Those who adhere to traditional ethical values commonly reinforce and develop traditions that promote sustainable development of mankind' [5].

CONCLUSION

Historically, the first principle of medical ethics is *primum non nocere*(*'first not do any harm'*). Students will learn about it during the first stages of their education and, primarily, in the course of bioethics. The norms and standards of bioethics become ethical guidelines that determine the further bedside education. In the process of education, students of medical universities urgently need the practical activity. They learn to contact with different patients, balance between a patient's fear and concern, convince that the selected therapy is rational, help a human being trust the doctor with the smallest nuances of life, which can influence the diagnosis, select the laboratory and instrumental diagnostics and treatment scheme. While communicating with patients, students understand the power of a word: it can help, motivate a patient for a positive outcome and cure him. That's why a doctor needs to be proficient in speech, have proper communication skills to make a good impression on patients and relatives, making them open up and trust patients.

Future physicians need to see on a daily basis how practicing physicians implement the standards of bioethics, learn from their experience and use it subsequently. Theory means nothing without practice just like pure practice means nothing without theory. It is important that students should be aware of the responsibility of the selected path. Only in this case the required result can be obtained.

Bioethics forms the basis of a medical student's life. Without the basis, it is difficult to become a professional in the future as successful doctor-patient communication is impossible without taking into account its bioethical, psychological and legal aspects. A student should know bioethical standards. The he will be able to make important steps on the path of learning the healing arts. According to Academician Chuchalin AG, 'the world of a doctor is complicated and often tragical, full of painful concern for own mistakes and constant search for solutions, which sometimes determine a human fate. Ethics and deontology are the essential features of a physician's moral activity. While speaking about ethical issues, we first of all mean the welcoming nature of a physician's activity. Empathy helps to implement the ethical standards of healing. A doctor has to deal with ethical issues related to the health values of a human every day; he takes a decision assessing what is good and what is bad' [6].

References

1. Simonyan RZ. Stanovleniye sistemy meditsinskogo obrazovaniya v Rossii: XVII — nachalo XX vv. Mezhdunarodnyy nauchno-issledovatel'skiy zhurnal. 2019; 84(6): 121–124. Russian.
2. Veresayev VV. Zapiski vracha. M.: Veche. 2022; 51. Russian.
3. Eticheskiy kodeks obuchayushchikhsya meditsine i farmatsii. Available from URL: https://rsmu.ru/fileadmin/templates/DOC/Local_Acts_Education/eticheskiy_kodex_obuchayuschikhsya_meditsine_i_farmatsii.pdf. Russian.
4. Petrovskiy BV. Deontologiya kak odin iz vazhneyshikh elementov vospitaniya v meditsine. Deontologiya v meditsine. 1988; 1: 352 s. Russian.
5. Chuchalin AG. Beseda s vrachom. Russkiye vrachi vracham … M.: Veche. 2022; 10. Russian.
6. Chuchalin AG. Beseda s vrachom. Russkiye vrachi vracham … M.: Veche. 2022; 35. Russian.

Литература

1. Симонян Р. З. Становление системы медицинского образования в России: XVII — начало XX вв. Международный научно-исследовательский журнал. 2019; 84(6): 121–124.
2. Вересаев В. В. Записки врача. М.: Вече. 2022; 51.
3. Этический кодекс обучающихся медицине и фармации. Режим доступа: [Электронный ресурс]. URL: https://rsmu.ru/fileadmin/templates/DOC/Local_Acts_Education/eticheskiy_kodex_obuchayuschikhsya_ meditsine_i_farmatsii.pdf
4. Петровский Б. В. Деонтология как один из важнейших элементов воспитания в медицине. Деонтология в медицине. 1988; 1: 352 с.
5. Чучалин А. Г. Беседа с врачом. Русские врачи врачам … М.: Вече. 2022; 10.
6. Чучалин А. Г. Беседа с врачом. Русские врачи врачам … М.: Вече. 2022; 35.