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И РОССИЙСКОГО НАЦИОНАЛЬНОГО ИССЛЕДОВАТЕЛЬСКОГО МЕДИЦИНСКОГО
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HUMANITARIAN ISSUES OF MEDICAL EDUCATION IN MODERN RUSSIA

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The article is devoted to the role of humanitarian education in medical universities of Russia. Events of recent years (lack of attention to the value orientation of students and, as a consequence, leaving the profession or feeling unsatisfied with it) that occurred in Russian healthcare determined the interest in this issue. The research data were obtained using the systemic approach. Owing to this, medical education was viewed as a non-integrated set of scientific, clinical proper and humanitarian knowledge and assessments. In this respect, the perspective of using humanitarian expertise of academic courses has been discussed. This was done to coordinate the efforts of socialization agents in development of professional orientation among medical students. A comparative analysis of the effect of High-Hume technologies and mentorship on the positive solution of this problem has been performed. A conclusion about the use of the complementary principle while implementing High-Hume and mentorship has been made. Search for the aggregator of integrative processes in medical and humanitarian preparation enabled to conclude that bioethics is a system-forming factor of developing professional orientation in medical education. Recommendations on the use of scientific and organizational achievements in bioethics in the practice of medical education have been developed.

Keywords: professional orientation, medical education, medical humanities, mentoring, High-Hume technologies, knowledge, values, bioethics, orientation, profession, bioethics

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ГУМАНИТАРНЫЕ ПРОБЛЕМЫ В МЕДИЦИНСКОМ ОБРАЗОВАНИИ СОВРЕМЕННОЙ РОССИИ

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Статья посвящена роли гуманитарного образования в медицинских вузах России. Интерес к данному вопросу определили события в отечественном здравоохранении последних лет — недостаток внимания к ценностным ориентациям студентов и, как следствие, уход из профессии или некомфортное пребывание в ней. Исследовательский материал был получен на основе применения системного подхода, что позволило рассмотреть медицинское образование как неинтегрированную совокупность естественнонаучных, собственно клинических и гуманитарных знаний и оценок. В связи с этим обсуждалась перспектива применения гуманитарной экспертизы учебных курсов, чтобы на основе полученных данных скоординировать усилия агентов социализации в формировании установки на профессию у студентов-медиков. Проведен компаративный анализ влияния High-Hume технологий и наставничества на позитивное решение этой задачи. Сделан вывод о применении принципа комплементарности в использовании High-Hume и наставничества. Поиск агрегатора интегративных процессов в медицинской и гуманитарной подготовке позволил сделать вывод о том, что системообразующим фактором формирования установки на профессию в медицинском образовании является биоэтика. Сформулированы рекомендации по использованию научных и организационных достижений биоэтики в практике медицинского образования.

Ключевые слова: установка на профессию, медицинское образование, медицинская гуманитаристика, наставничество, High-Hume технологии, знания, ценности, биоэтика, установка, профессия, биоэтика

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In the post-Soviet era of Russia, medical education suffered certain setbacks. First, sub-internship was cancelled. The reasons were formulated in an unclear way. Then internship was eliminated. Extramural postgraduate training program was cancelled as well. At the same time, the postgraduate program itself became equivalent to the specialist program with research proper being pushed to the background and attending lectures being strictly controlled. Simultaneous, almost twice reduction of the period of study at medical colleges unwittingly suggests an act of intellectual sabotage against medicine.

Not excluding a quite possible implementation of the destructurization plan of Russian healthcare as a social institution, it would be logical to assume that all the enumerated activities were aimed at cost saving, whereas professional damage was not taken into consideration, as a number of subjects was reduced at the expense of non-core disciplines. Temporary transition to remote learning due to adaptation to COVID-19 conditions only made things worse [1]. Especially because this kind of learning of non-core disciplines became permanent. It happened not at every

university and college, but frequent enough not to pay attention to this [2].

This results in an acute shortage of doctors and nursing personnel in Russian healthcare. According to the Federal Compulsory Medical Insurance Fund (FCMIF) [3], the total number of doctors was 145,010 people by the end of June 2022. It was decreased by 1.9 percentage points as compared to the beginning of the year. The total number of nursing personnel decreased by 2.3% and amounted to 371,637 people. This was stated by Chamber of Accounts in the FCMIF budget progress report in 2022 [4].

In fact, the country lost 2,756 doctors and 8,695 nurses within six months of 2022. How could the fact be associated with reduction in the time spent on preparation of medical professionals? Competition in medical educational institutions (both universities, and colleges) is consistently high. Where are the qualified medical personnel then? They master other professions or switch to private medical practice. As private medicine places high demands on professionals, a young graduate can hardly expect a warm welcome. It is known that many part-timers such as doctors and nurses from state and municipal medical organizations are in private practice. Working there has a number of advantages. Thus, private medicine is not at risk of staff shortage. At least, this applies to large network players at the private medicine market [5]. The main reason for leaving the profession or switching from state medicine to private practice is financial one. Other reasons include better labor conditions and possibility of self-realization [6].

All these reasons are obvious enough. However, they are manifested differently for various people. There is, however, an option of leaving state medicine or medicine in general. It occurs when professional orientation is lacking. According to Pavel D. Tishchenko, outstanding Russian scientist in bioethics, healing is practical mercy [7]. Capacity for it is definitely congenital. Nevertheless, it should be executed, developed and fixed, but how exactly?

RESULTS AND DISCUSSION

The ratio of medical knowledge and their socio-humanitarian orientation

Gaining professional knowledge is the main objective of medical and other education. Professional teachers deal with this task. In medicine, teachers play a binary role, as they teach both theory, and practice. A special role belongs to those clinicians who supply patients with real medical aid in collaboration with students, residents and postgraduate students. The essence of their professional activity is to develop skills and abilities and provide knowledge to future physicians. However, representatives of non-core, primarily humanitarian disciplines, are responsible for how the knowledge will be used. An adequate professional orientation should be developed to make the obtained knowledge useful but not harmful. Michel Foucault wrote as follows: ‘a physician holds a special place in any society and any civilization: he attracts public attention everywhere and is almost irreplaceable. A physician’s word can’t come ‘from nowhere’: its significance, effectiveness, therapeutic abilities and general conditions of existence, just like the words of medicine itself, can’t be separated from the status of a certain person who articulates, proclaims and confirms the legal right to diminish sufferings and prevent death’ [8, 5].

Underestimation of humanitarian knowledge means that medical teachers distance themselves from transmission of valuable information when communicating with their students by default or just provide short examples of it, which are easy to forget. At the same time, humanitarian teachers are very limited in using medical data that should be analyzed to solidify the system of values. The students do not believe humanitarians who are not medical professionals. Medical teachers try to avoid social issues not because they do not know much about them, but because they are willing to use the class time to ensure better understanding of professional requirements. Thus, it is possible to set a task of integration of special medical knowledge and humanitarian assessment of their use [9, 10]. To determine the ways to solve the task, it is necessary to conduct a preliminary humanitarian expertise of the educational process. It is necessary to find out how they present the social meaning of this profession in the courses of academic subjects at special departments and how the professional context of medical education is presented within a humanitarian discourse.

The method of humanitarian expertise has not been developed enough yet to make the application of certain templates possible. Moreover, polyvariety of humanitarian knowledge implies a difference in explication of its types to the use in relation to medical disciplines. Thus, such a discipline as Public Health and Healthcare Organization considers medicine as a social institute, whereas this approach would be inappropriate for the disciplines of a morphological profile. In this case, philosophical concepts of bios would be useful as basic ones. The philosophy itself would be taught as work-related, i. e., as *philosophy of medicine* [11].

Another very complex issue relates to the criteria of humanitarian expertise. What can be considered useful or doubtful? The requirements are not developed yet. So, it is logical to use the principle of conventionalism. Meanwhile, different educational medical organizations can have a different list of criteria. This approach corresponds to modern requirements of WCF, where universities are granted with extensive rights while taking decisions on compilation of training programs and courses.

A humanitarian expertise should not be a calendar event. Its object can include different structures at different times. It is better to start with learning the views of students and teachers regarding which issues seem more interesting to them in a professional way or in a socio-humanitarian area. The data can be obtained through a simple survey. Depending on the results, it is possible to shift to other stages such as analysis of working programs, determining the areas of behavioral risks, educating teachers (teaching doctors about humanities, and teaching humanitarians about the medical issues that can be useful while implementing academic courses). Medical humanities are a field of doctor-humanitarian joint activity. But this is not a mechanical sum of ‘activities’, this is art, discussion and cooperation. So, such forms of cooperation as elements of web-based learning [12], lectures and practical classes ‘for two’ (lecture as a dialogue between a medical teacher and a humanitarian teacher) are extremely useful. As extracurricular activities used in our universities and colleges are abundant, there is no need to invent new ones, it’s enough to use those available with a focus on medical and humanitarian content.

So, the humanitarian expertise has been conducted, conclusions have been made, and we know what should be done by whom; can our activities help obtain the positive and active orientation to the profession that started it all? The key aspect is interiorization of true knowledge and proper assessments by every student, resident and postgraduate student. It is easier with knowledge, as we can check whether it

is true. But only knowledge is not enough to form an adequate idea of the world and live in it. Orientation in the space of values is required (evaluation activity).

In medical education, axiological plots are mainly presented in human sciences. But there is one thing to mention. Assessments can't be logically deduced from knowledge (unlike new knowledge). Assessments are empirically untestable (only truth/falsity can be tested). Value judgements are not falsified (because they depend on the personality of the assessing person). The assessments are unexplainable (when they are tried to be explained, they stop being assessments and become knowledge). The assessments do not imply direct and indirect empirical confirmation. Hume's principle, stating that assessments and standards can't be deduced from facts, is accepted as an axiom.

Thus, the risk of taking erroneous decisions based on wrong assessments is much higher than the risk of taking erroneous decisions based on false or insufficient knowledge. What can be done about it? More perfect methods of formation of professional orientation associated not with financial considerations, but with the feeling of mercy, compassion and love for the neighbor, are required. But how can novel technologies correspond to humanitarian purposes of medical education?

Hi-hume-technologies and/or mentor's personality?

A student can be influenced in numerous ways. It is an axiom. The old model of medical education means transition of knowledge and practice organized following the principle of 'Do What I Do'. Nowadays there are methods and techniques that enable to program a future specialist's behavior in accordance with requirements and expectations of the society. Can their inclusion into the educational process bring their orientation into focus and improve effectiveness? The highest expectations can be associated with High-Hume technologies.

'High-humanitarian technologies (High-Hume)' is a new term. There is a connection with an earlier and widely spread 'High-Tech' term. But High-Hume technologies are related not to technological, but to social and psychological resources [13]. The technologies produce a direct effect on consciousness. Initial objective of their development and use included the sphere of consumption of goods and services.

Some researches even believed that they were a tool of marketing. However, the functions changed as soon as they were developed: now, marketing can be a variant of High-Hume. The mechanism of implementation of information and psychological, psychoanalytical, neurolinguistic and similar technologies reminds of logistics of personalized medicine, when an active drug is selected or developed based on individual features of the target typical of a certain group of patients. So, High-Hume technologies focus on group orientation, experience, world view and cultural patterns of a targeted object. Appealing to the basic personality components, the personality is affected using psychological, political, social, culturological and other humanitarian methods. If these technologies have been used for purely commercial purposes, other purposes such as political ones gradually emerged. There is a question: why can't the technologies be used to form respective educational and professional orientation among future doctors? It will be more effective than educating activities or memorization of learning material. Importantly, a student's personality undergoes no changes, it is the emphasis placed on the world-view and behavior that has been changed. The approach of developing professional orientation seems effective. Nevertheless, there is some risk that makes the approach doubtful.

High-Hume technologies have been known for a long time but had another name (behavior modification). They were simpler and more primitive, but still dealt with the same goals as now. Negative attitude to behavior modification was explained by the unwillingness of people to be puppets. Now, they still don't want it. High-Hume tech subjects refer critics to obtaining an informed consent from the involved objects, though the procedure was not processed and is rarely applied, as it can influence the result. It can be said that humanitarian knowledge and their value-based arrangement using High-Hume technologies managed to find their place in medical education. At the same time, they produced a risk of violating the principle of respect for autonomy of not a patient, but of a doctor who teaches and the doctor's students.

Is there an alternative to the High-Hume that addresses the problems of developing the orientation toward the profession of future doctors? Yes, there is. It's called mentorship [14]. The social institute of mentorship as a phenomenon of continuous medical education has been considered in various studies. Now, there is no information in literature stating what is the advantage of this form of interiorization of medical knowledge and values over cutting-edge High-Hume technologies. Comparison can be as follows:

- High-Hume technologies focus on a group consisting of people with similar social and psychological characteristics, whereas mentorship is being implemented through personal communication of two individuals;
- Using digital technologies, High-Hume develops humanitarian standards of professional orientation, mentorship, and unique capabilities, creativity and ability to deviate from standards in favor of a patient;
- High-Hume uses data banks, whereas a mentor utilizes personal exclusive experience;
- High-Hume uses ethical components of a medical profession as a means of orientation development; in mentorship, medical ethics is included into profession and is of a theological nature.

Thus, while preparing future physicians, mentorship is more preferable than High-Hume technologies, mainly for moral reasons. However, mentorship has similar shortcomings. A mentor helps young and untrained doctors. They already have certain orientation, which is difficult to change. That's why mentors should be selected among practical doctors at clinics, where students arrive and get access to the patients. There they interact with a practicing physician who doesn't estimate their knowledge, doesn't introduce to the theory, but just accomplished the work in the presence of a student, shows and explains what has been done, narrates about practical cases and just talks about life.

Shortage of mentors is another challenge. Not every practicing physician can fulfill the function, and some of those who can are not willing to do it. Forcing is not effective in this case, as it is a vicious moral requirement. Thus, staff challenges in mentorship are both of a production, and moral sense. They are not decided yet.

CONCLUSIONS AND RECOMMENDATIONS

Integrative function of bioethics in the educational medical space

Ethical parameters of developing a professional orientation are of fundamental importance while selecting the development methods. All the abovementioned issues form a single complex with biomedical ethics being its system-forming factor. First, it is an essential constituent of this profession. Second, professional

orientation has moral content. Thus, we can sum it up and suggest some recommendations.

1. Leaving profession is mainly associated with an unstructured value orientation. So, continuity of ethical content in all studied disciplines and all directions (college, higher education, graduation, residency, postgraduation, continuing medical education) is required. A continuous program of ethical preparation in medical education should be developed and implemented.
2. Among all humanitarian disciplines, only bioethics embraces scientific, clinical proper and humanitarian knowledge and assessments. Moreover, only bioethics can integrate knowledge and assessments. However, only knowledge is given priority in practical medicine (for instance, practice of implementing Clinical Recommendations and their content). So, the system of continuing medical education should contain a course of advanced training in biomedical ethics.
3. Bioethics contains a clear and well-tested system of ethical expertise in medicine [15]. Due to adaptation of the social institute of medicine and healthcare to new realities of science and social life, it became evident that the expert space should be expanded shifting from the ethical expertise proper to the humanitarian expertise. Thus, ethical committees should focus on humanitarian expertise in medicine, reconsider the related Provisions and introduce the article about the status of these Committees into Federal Law No. 323-FZ.
4. Bioethical content of using High-Hume technologies and the institute of mentoring require improvement and social assessment. Thus, it would be useful to conduct ethical expertise of using High-Hume technologies and applied mentoring techniques in medical education to provide the interested subjects with recommendations on their proper and safe usage.

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“LIBRARY OF BIOETHICS”: CONTRIBUTION TO THE DEVELOPMENT OF EDUCATION (REVIEW OF A MULTI-VOLUME EDITION) M.: VECHE, 2019–2022; VOLUMES 1–10

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The published review is devoted to ten-volume edition entitled Bioethics Library published by Veche publishing house. The series was edited by Academician Chuchalin AG. It consisted of various works related to bioethical issues. The edition is mainly intended for students and teachers of bioethics of Russian medical universities. The series has a wide historical framework. It examines the works by Avicenna and Immanuel Kant, translated books by Sweden researchers Johansson I and Lynøe N. Texts by Russian physicians and thinkers (Berdyayev NA, Veresayev VV, Uglov FG, Botkin ES, Voyno-Yasenetsky VF (St. Luka Krymsky), Pirogov NI, Pavlov IP, Koni AF, Ilyin IA, Metropolitan Antony Surozhsky, etc.) are published as well. A collection of official documents on bioethical regulation is presented as a separate volume. The edition comprises self-evaluation questions. The texts included into the Bioethics Library make the readers familiar with the history of bioethics building and formation as an anthropologic project. Bioethics is based on the value of life and human integrity, it protects the human being and society, and, as a result, possesses regulatory functions. In the edition, special attention is paid to Russian authors and their view of bioethical issues. It is assumed that examination, popularization and content analysis of the series are particularly relevant within the context of national bioethics development.

Keywords: bioethics library, medical ethics, an anthology of bioethics, Russian bioethics

Author contribution: equal

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«БИБЛИОТЕКА БИОЭТИКИ»: ВКЛАД В РАЗВИТИЕ ОБРАЗОВАНИЯ (РЕЦЕНЗИЯ НА МНОГОТОМНОЕ ИЗДАНИЕ) М.: ВЕЧЕ, 2019–2022; ТОМА 1–10

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Публикуемая рецензия посвящена десятитомному изданию «Библиотеки биоэтики», которое вышло в издательстве «Вече». Серия вышла под редакцией акад. А. Г. Чучалина и включила различные труды, затрагивающие биоэтические проблемы. Издание предназначено в первую очередь для студентов и преподавателей биоэтики российских медицинских вузов. Исторические рамки серии широкие: в нее вошли труды Авиценны и Иммануила Канта, перевод книги современных шведских исследователей И. Йоханссона и Н. Линё. Публикуются тексты русских врачей и мыслителей: Н. А. Бердяева, В. В. Вересаева, Ф. Г. Углова, Е. С. Боткина, В. Ф. Войно-Ясенецкого (свт. Луки Крымского), Н. И. Пирогова, И. П. Павлова, А. Ф. Кони, И. А. Ильина, митр. Антония Сурожского и др. Отдельным томом издан сборник официальных документов по биоэтическому регулированию. В издание включены вопросы для самоконтроля по прочитанному материалу. Тексты, собранные в томах «Библиотеки биоэтики», направлены на ознакомление читателей с историей построения и развития биоэтики как антропологического проекта. Биоэтика основывается на ценности жизни и целостности человека, стоит на защите человека и общества и, за счет этого, обладает регулятивными функциями. Особое внимание в издании уделено отечественным авторам и их взгляду на биоэтические проблемы. Представляется, что изучение, популяризация серии и ее содержательный анализ особенно актуальны в контексте разработки национальной биоэтики.

Ключевые слова: библиотека биоэтики, медицинская этика, антология биоэтики, российская биоэтика

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The last volume of Bioethics Library — issues in bioethics released since 2019 — was published in 2022. The ten-volume edition was issued by the known Russian Veche Publishing House specializing in historical literature. Bioethics Library edited by Academician A. G. Chuchalin, an outstanding Russian pulmonologist, included various publications related to bioethical issues.

This review with a summary of the examined series only is intended to make the outstanding edition more popular, draw attention of those readers who are interested in development of Russian bioethics, and teachers of bioethics from Russian medical universities, in particular.

Bioethics Library was created with the support of the Commission of the Russian Federation for UNESCO and Russian Academy of Science. Academician A. G. Chuchalin (Vice-President of the UNESCO Intergovernmental Bioethics Committee and Chairman of the Russian National Bioethics Committee) and sponsors involved by him took an active part in the edition publication. The series is mainly intended for medical students, teachers and doctors [1]. The purpose of the series is to increase the quality of medical and humanitarian education in the field ethics by making the readers familiar with the unique experience and publications of Russian and foreign doctors, scientists and writers [1].

It is noteworthy that no volume of the ten-volume edition went on sale; the series is not sold at book stores. There is an online version of the third volume, but other books of the series are not published online [2]. The many-volume

set arrived to the libraries of the Russian Universities. In Moscow, it can be found, for instance, in the Russian State Library (6 volumes out of 10 are presented in the catalog of the Scientific Library of the Moscow State University, 7 volumes out of 10 are kept in the Central Scientific Medical Library). In Saint-Petersburg, the collection is available in the Russian National Library. The many-volume set is also available in some other libraries of Russia. It is not easy to find it in e-catalogs: searching through bases of University libraries is frequently limited for public users. According to the publishers, medical universities of Belarus and Kazakhstan will be among the first to get the ten-volume Bioethics Library edition [3].

Thus, a series of Bioethics Library is a rarity. At the time of publication of the article, Veche publishing house is busy with preparing an electronic ten-volume edition. It is remarkable that Academician A. G. Chuchalin, editor-in-chief, has prepared an adapted version of UNESCO bioethics program for Russian medical universities (published in the seventh volume of the series). According to Academician A. G. Chuchalin, bioethics program should be continuous (from year 1st to year 6th) and include post-graduation education, as 'a physician's education, including ethical one, is ended with the physician's death' [2]. The ten-volume Bioethics Library edition should serve as a training aid for teaching biomedical ethics at higher medical institutions. As the series is intended for students, every volume contains self-assessment questions (except for Volume 6 devoted to Kant without the questions).

Chronological frames of the series are rather wide. The majority of the texts relates to the XIX century. However, separate volumes are devoted to Avicenna and Kant. Owing to that, the Bioethics Library also includes works of the Middle Ages, classical texts of German idealism, and works of modern Sweden scientists Johansson I and Lynøe N. Another volume is devoted to various official documents accepted on the issues of bioethical regulation. Nevertheless, the major part of the anthology — 6 volumes — is devoted to works of Russian authors of the XIX, XX and XXI centuries. This gives the edition special importance in comprehending history and peculiarities of Russian bioethics.

The Bioethics Library collects the works of doctors and philosophers speculating about the medical and research ethics and rules of experimenting with a human being and animals. Global challenges of the XXI century associated with development of new genetic and reproductive technologies and AI technologies are addressed as well. Works of such doctors as Botkin ES, Uglov FG, Veresayev VV, Voyno-Yasenetsky (St. Luka Krymsky), et al. are published in the edition.

STRUCTURE OF THE BIOETHICS LIBRARY

The ten-volume edition has three parts.

The first part is general. It consists of two volumes. The first volume contains numerous Russian and international legal documents related to bioethics, and UNESCO Guideline on Communication with Bioethical Committees [4]. The second volume within the first part includes a collection entitled Russian Physicians to Physicians [5].

The second part is devoted to philosophical foundations of bioethics. It consists of three volumes such as Kant's Lectures on Ethics, Medicine and Philosophy: Introduction to the XXI century by Johansson I. and Lynøe N., and works by Berdyayev N. A. (On the Destination of a Human Being, Self-Exploration) [6–8].

The third part is special. It is aimed at ethical preparation to communication with patients. It consists of 5 volumes such as Moral Foundations of Medicine by Avicenna (Ibn Sina), Physician Yevgeny, Passion Bearer, Doctor Botkin ES, A Physician's Notes by Veresayev VV, I Liked the Suffering by Voyno-Yasenetsky VF and The Heart of the Surgeon by Uglov FG [9–13].

The order, in which the volumes were issued and numbered, is not associated with the abovementioned division of the collection into three parts. So, it is appropriate to mention the volumes not in numerical order, but in accordance with the thematic division introduced by A. G. Chuchalin [2].

THE FIRST PART OF THE SERIES. COLLECTIONS

The first part of the series is entitled 'General' by the editor-in-chief. It includes volumes 3 and 7. Both volumes are collections (as every other volume is devoted to one personality only).

Volume 3, Bioethics and Global Challenges. Documents and Speculations [4]. Sayamov YuN, Cand. Sc. History, Head of the UNESCO Department for Global Issues of the Faculty of Global Processes of Lomonosov Moscow State University, is the author of this volume, which is the most extensive of all ten. The most part of the book is occupied by various documents devoted to bioethical regulation. It is for the first time when all basic documentation related to bioethics is united within the same edition in Russian literature. Thus, the edition included 25 most important documents devoted to bioethics and accepted by UNESCO, WTO, Council of Europe and other international companies. Russian documents such as The Oath of the Soviet Doctor, The Oath of the Russian Doctor, etc. were published in addition to international documentation. Notably, the collection included not only official international and national documents, but also some documents which are considered by the authors to be essential for Russian bioethics.

It is included into the Ethical Physician's Code of the Republic of Tatarstan, Code of Ethics and Official Conduct for Employees of Saint-Petersburg Municipal Outpatient Clinic No. 98 and other remarkable documents regulating the activity of physicians and medical institutions.

A detailed guideline to communication with bioethical committees in five parts developed by UNESCO was published in the concluding provisions of volume 3. The first three parts are issued in Russian. They describe the mechanism of creating bioethics committees, the manner of their functioning, and procedures of teaching the committee participants. Parts 4 and 5 hereof are in English; they are devoted to the interaction of bioethics committees with the country and society.

Meanwhile, volume 3 is not compiled of various documents. The chapters written by Sayamov YuN are published as an integral collection. Volume 3 also includes the article by Lopukhin YuM entitled Bioethics in Russia that has been published in the Annals of the RAS [14]. Detailed speculation about development of bioethics in Russia, activity of Russian bioethics committees and teaching bioethics at Russian Universities is provided in the book.

Volume 7, Russian Physicians to Physicians, embraces numerous works of outstanding Russian doctors of the XIX, XX and XXI centuries [5]. The works by A. G. Chuchalin are published in the first part of the volume. They include Conversation with a Doctor with a list of various questions a patient is asked by his/her doctor. The bioethics and human rights author training course (adapted for Russian medical universities, UNESCO program type) is published as well. The

second part of the collection includes the works by outstanding physicians, philosophers, writers, priests, lawyers (Mudrov MYa, Pirogov NI, Pavlov IP, Petrov NI, Blokhin NN, Botkin ES, Koni AF, Ilyin IA, Bilibin AF, Uglov FG, Blokhin NN and Metropolitan Antony Surozhsky.

Full version of the book can be found on the site of the Far-Eastern State Medical University [15].

THE SECOND PART OF THE SERIES. PHILOSOPHICAL FOUNDATIONS OF BIOETHICS.

The second part of the many-volume set has 3 volumes.

Volume 6 includes Kant's Lectures on Ethics [6]. The edition begins with a foreword Ethics of Goodwill written by Academician Huseynov AA. Kant's Lectures on Ethics are published in Russian. They are translated by Sudakov AK and Krylova VV (with commentary by Sudakov AK). The edition also embraces such works as the Groundwork of the Metaphysics of Morals (remarks are provided by Skripnik AP) and the Critique of Practical Reason by Kant. Volume 6 has the same content and structure as Kant's Lectures on Ethics, which was published by the Republic publishing house in 2000 and 2005 [16, 17].

Volume 1, Medicine and Philosophy: Introduction to the XXI century, is a translation of Medicine & Philosophy. A Twenty-First Century Introduction written by Johansson I. and Lynøe N. [7, 18]. The book is available in Russian for the first time. According to the authors, the edition describes the issues which are common to medicine, medical ethics, medical information and philosophy. It begins with the foreword of A. G. Chuchalin to translation into Russian. The foreword presents a work published by Swedish scientists and contains a summary of the chapters. A. G. Chuchalin says that Medicine and Philosophy is one of the best teaching aids about the history of philosophical trends in science and medicine, modern interpretation of the issues of medical ethics and bioethics, taxonomy and partonomy. Meanwhile, the book can sometimes be used as a guideline for teachers as it contains the following chapters: 'What is a science fact?', 'What is a scientific argument?', 'Phenomena of placebo and nocebo', 'Pluralism and medical sciences', etc.

Volume 10, On the Destination of a Human Being. Self-exploration, includes the works by Berdyayev NA [8]. It contains the following publications: On the Destination of a Human Being. The Experience of Paradoxical Ethics (1931) and Self-Exploration (1940). The book is accompanied with a foreword entitled as Three Ethics and Three Freedoms of N. Berdyayev. Its authors (A. G. Chuchalin and E. V. Bobkov) draw attention to Mr. Berdyayev's original ethics, where ethics is a doctrine of man. It focuses on Mr. Berdyayev's philosophical autobiography, who emphasized the significance of human freedom.

According to the authors, the topics covered by Mr. Berdyayev are similar to the topics of bioethics and human rights course. Its program was published in volume 3 of the ten-volume edition [2, 4]. In particular, Mr. Berdyayev speculates what ethics is; he also discusses human dignity, human rights, and human personality autonomy.

THIRD PART OF THE SERIES. EXPERIENCE OF PHYSICIANS

The third part of the series devoted to preparation of a physician to communication with patients includes 5 volumes.

Volume 9. Avicenna. Moral Foundations of Medicine is prepared by the UNESCO bioethics department at the Kazan State Medical University [9]. Heritage by Ibn Sina is presented in the book within the context of the Middle Ages. The volume begins with the introduction by Prof. A. S. Sozinov, Rector of the University, and includes a number of articles such as Culture, Medical Science and Practice of the Arabian East in the Middle Ages (Gurylyova ME, Mukhamedova ZM), Ibn Sinna's Life Path (Ternovsky VN), Arabian and Muslim Philosophy of the Middle Ages (Nezhmetdinov FT), Avicenna's Ethical Principles (Nezhmetdinova FT, Abrosimova MYu, Mukhamedova ZM), Avicenna's The Canon of Medicine: The Bridge between the Ancient and Modern Medical Science (Mamedov MN). It is noteworthy that almost all articles of this collection (except for the last one) have self-evaluation questions. Avicenna's texts devoted to medical and ethical issues are published in the Primary Literature section and subsequent chapters. The book concludes with a brief glossary of used terms and notions.

Volume 2, Physician Yevgeny, Passion Bearer, Doctor Botkin ES, is devoted to Yevgeny S. Botkin, a son of famous physician Sergey P. Botkin [10].

Botkin ES was a court physician for Tsar Nikolas II. He was murdered in Yekaterinburg in 1918 together with the members of the Tsar's family. In the introduction, A. G. Chuchalin mentions three reasons why Dr. Botkin's heritage is important for modern medicine. First, he was loyal to the principle of the Russian medical school stating that it is the duty of a doctor to provide medical assistance to a sick person (irrespective of the patient's status). Second, the issue of doctor-patient communication holds an honorable place in his heritage. Love for the sick person is mainly displayed through the dialogue. It makes treatment successful. Third, Botkin ES's behavior can serve as an example in the issues of medical ethics as well: he has never created conflicts.

The book begins with the introduction by Bobkov EV entitled The Happiest Preserve of the Russian Citizen in Really Difficult Times (Dr. Botkin's Virtue Ethics). Of particular interest are Dr. Botkin's letters and lectures published for the first time. His speeches such as Patients at a Hospital and What does It Mean to Spoil Patients? were included into the edition. The letters to his wife written in 1904–1905 (Dr. Botkin served as a military doctor during the Russo-Japanese war) and letters to children are published as well. The edition also includes a number of biographic materials and articles devoted to Botkin ES, numerous pictures and ends with a list of test questions and answers to them.

Volume 8 includes A Physician's Notes by Veresayev VV [11]. The edition consists of the book written by a famous Russian physician (A Physician's Notes), his articles, fragments from the Live Life book (the first part is entitled About Dostoevsky and Lev Tolstoy), and his Literary Memoirs. The book begins with a foreword by Belevsky AS, Dr. Med. Habil. According to him, the issue of medical error, medical practice and attitude of a physician to material remuneration are considered essential by Dr. Veresayev. The edition ends with a list of issues for discussion offered to the reader.

Volume 4, I liked the Suffering, includes the works by an outstanding surgeon, Dr. Med. Habil., Archbishop of Crimea Luka Krymsky (Voyno-Yasenetsky VF). He was one of the most renowned doctors and priests of the XX century [12]. The book includes three main publications by Archbishop Luka such as I liked the Suffering, About the Spirit, Soul and Body and Science and Religion. The book begins with a foreword entitled Archbishop Luka and includes the author's biography, and a list of self-evaluation questions.

Volume 5, The Heart of the Surgeon, represents a famous book of Fyodor G. Uglov, a surgeon, social activist and writer (1904–2008) [13]. The book is accompanied with a foreword by Bagnenko SF and Kutykova IV entitled as Philosophical and Bioethical Aspects of Dr. Uglov's Spiritual Heritage. The authors mention that the book is about medical ethics (its formation, development, basic values, rules and norms), basic principles and rules of biomedical ethics, models of doctor-patient relations, ecological problems and bioethics ratio. The edition starts with the following foreword: 'The book describes own experience. <…> It is neither special research, not memoirs. It is rather a story about hard and noble work of a surgeon, which is so vital to the society'. Recollections of Dr. Uglov's colleagues are included into the book.

GENERAL DESCRIPTION OF THE SERIES

All texts included into the Bioethics Library editions have something in common: they make readers familiar with the history of building and development of bioethics as an anthropologic project. The task of bioethics is not just to justify the existing practices or designate medical, healthcare or scientific research risks. Bioethics is based on the value of human life and integrity, it protects a human being and society, and due to this, possesses regulatory functions.

Thus, a philosophical block of texts by I. Kant and N. A. Berdyayev, which, at first glance, is not directly referred to the ethics of medicine and biotechnologies, creates a powerful ontological and axiological foundation to discuss the issues associated with the ethics of a physician's duty, essence of a human life, ideas of the human nature and nature of the disease. It is not accidental that the books by I. Johansson and N. Lynøe, representatives of modern western bioethics, are included into the series as their works represent an example of profound methodological sociohumanistic analysis of modern science and medicine. In particular, it justifies the necessity of bioethical regulation of modern practices. The approach offered by the Swedish researchers have a pronounced value orientation. When assessing ethical issues, the authors stick to relativism, which is frequently widely spread in the western bioethical discourse.

The books of the series contain numerous works written by doctors, outstanding Russian specialists, who describe their long-term professional experience. It makes the reader think that the treatment process is very sensitive, whereas a professional physician has a clear moral position.

The Library of Bioethics creates a single set of basic works of Russian authors, which are essential as a source of comprehension of value foundations of practical medicine. The authors' works set the direction for ethical assessment, social and humanistic expertise and ethical and legal regulation of biotechnological projects in Russia. They can also be used in assessment of the foreign bioethical concepts from the point of view of historical and cultural foundations which are traditional for Russia.

Medical students study bioethics on a compulsory basis. The Bioethics Library will certainly be useful both for students and teachers of bioethics. The bioethics program published in volume 7 will facilitate compilation of own programs by teachers. Self-evaluation questions at the end of every volume are good for academic work. Works of outstanding Russian physicians will pay attention of students to the Russian context, and theoretical notions of bioethics will be demonstrated in practical medical experience.

New medical and other technologies interfering into the human nature require continuous ethical recognition, creation of new texts, including philosophical, regulatory and legislative ones. The authors of the Bioethics Library series offer texts for subsequent working in this direction. It is assumed that studying and popularization of the Bioethics Library and its meaningful analysis are particularly relevant in the context of national bioethics development.

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ORGANIZATION OF THE SOCIAL AND PSYCHOLOGICAL SUPPORT SERVICE AT A HIGHER EDUCATIONAL INSTITUTION (BY THE EXAMPLE OF THE YAROSLAVL STATE MEDICAL UNIVERSITY)

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The article presents the rationale for formation of the social and psychological support service at a higher educational institution by the example of the Yaroslavl State Medical University (YSMU). The service is of particular importance, as the initial period of study at a university is associated with significant shifts, breaking of pre-existing stereotypes, stress, high anxiety and internal stress. This is a complicated stage of a human life, when not only physical, but also mental health of a person is finally formed, needs, motivation and personality of a future doctor are created, affecting the rest of the life. So, a higher institution is interested in the formation of a favorable educational and pedagogical environment, preservation and strengthening of students' health, better effectiveness of education and quality of knowledge, and, thus, prevention of being expelled from the University. It should be noted that the need in this area development is confirmed by survey of students from the YSMU. The obtained results confirmed that the students were interested in the development of social and mental aid and support. It was the basis for creation of the Center for Social and Psychological Support at the University. According to the survey, the students need this kind of aid. Supply of students with practical aid, social support and support of mental health of students, and prevention of social disadaptation are the main problems solved with the help of professionals from the Center for Social and Psychological Support of the Yaroslavl Medical University.

Keywords: social and psychological support, students, survey, data research, medicine

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ОРГАНИЗАЦИЯ СЛУЖБЫ СОЦИАЛЬНО-ПСИХОЛОГИЧЕСКОГО СОПРОВОЖДЕНИЯ В ВУЗЕ (НА ПРИМЕРЕ ЯРОСЛАВСКОГО ГОСУДАРСТВЕННОГО МЕДИЦИНСКОГО УНИВЕРСИТЕТА)

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В статье представлено обоснование создания службы социально-психологического сопровождения в высшем учебном заведении на примере Ярославского государственного медицинского университета. Особая значимость данной службы определяется тем, что начальный период обучения в вузе связан с социальными переменами, «ломкой» прежних стереотипов, стрессовыми ситуациями, высокой тревожностью и внутренним напряжением. Это сложный этап в жизни человека, когда окончательно формируется не только физическое, но и психическое развитие человека, формируются потребности, мотивации и личность будущих врачей, что отражается на всей дальнейшей жизни. Поэтому высшая школа заинтересована в создании благоприятной образовательно-педагогической среды, сохранении, укреплении здоровья студентов, в повышении эффективности обучения и качества знаний, и тем самым в предотвращении отчисления их из вуза. Стоит заметить, что потребность в развитии данного направления подтверждена данными анкетирования студентов ЯГМУ. Полученные результаты подтвердили заинтересованность студентов в развитии социально-психологической помощи и поддержки. Это явилось основанием для создания в вузе Центра социально-психологического сопровождения. Потребность в этом виде помощи подтверждается и данными опроса обучающихся. Оказание практической помощи студентам, социальное сопровождение и поддержание психологического здоровья обучающихся, профилактика социальных дезадаптаций — главные задачи, которые решаются с помощью специалистов Центра социально-психологического сопровождения Ярославского медицинского университета.

Ключевые слова: социально-психологическое сопровождение, студенты, опрос, данные исследования, медицина

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Preparing qualified doctors is one of the most important areas of implementing state programs and national projects in the Russian Federation [1].

Transformation of the society is accompanied by modernization of higher education, whereas modern conditions place high demands on future medical professionals, their education, health and intellectual capabilities. Having entered a higher educational institution, a student, who was at school yesterday, comes across numerous challenges, both objective, and subjective, and finds himself/herself in a new social, psychophysiological, domestic and climatic environment [2].

According to Repyova NG, the initial training period at a higher educational institution is associated with social changes, breakage of previous stereotypes, stressful situations, high anxiety and internal stress [3].

It is a difficult stage in the life of a person, when not only physical, but also mental health is finally formed, needs, motivation and personality of a future doctor are created, affecting the rest of the life. So, a higher institution is interested in the formation of a favorable educational and pedagogical environment, preservation and strengthening of students' health, improvement of education and quality of knowledge, and, thus, prevention of being expelled from the University.

Many professionals consider the educational and pedagogical process of a higher educational institution as a factor aimed at making students independent, and as an active creative adjustment of students to the conditions found

at a higher educational institution, including the ones used while solving difficult situations, and development of moral and personal qualities. However, adaptation of students at a higher educational institution is normally a problematic aspect of higher education. Attention is mostly paid to the educational process, whereas social issues and well-being of students are given less attention [2–4].

The issues of adaptation of young people to the educational and pedagogical environment are especially essential while preparing future healthcare professionals. The level of professional preparation and, thus, quality of rendered medical services depend on the way a young doctor or pharmacist is prepared. Soviet experience is especially illustrative in this regard, when massive training of medical personnel allowed to solve the problem of bad medical aid in the rural areas [5].

Thus, at present, it is necessary to create universal conditions for full personal and subjective development of medical professionals, when skills and abilities of the organization of mental activity and calling to the selected profession are being formed. As social and psychological factors that include the need in adaptation to novel social conditions belong to an essential adaptation factor for the first-year students, social and psychological service of a medical institution can provide direct assistance to them [6]. It testifies to a necessary examination of the need of those studying at a medical university in the formation of a comfortable social and psychological environment. It is done to reveal and solve the students' problems that influence the quality of education and to create proper conditions for the preparation of future medical professionals.

The purpose of the research is to examine the interest of the students of the YSMU in the face of the University-based social and psychological service development.

MATERIALS AND METHODS

The research was conducted to examine the interest of students in the social and psychological service formation and development. The research was participated by 863 students from the YSMU aged 17 to 29 with the mean age of 22.63±1.58 years (660 young women, 203 young men). The survey was conducted using a special questionnaire. Its questions were intended to discover the interests of students in the formation and functioning of the social and psychological service.

The students had to answer 11 questions.

1. Did you have any difficulties in learning in your 1st year of studying?
2. Did you have any trouble with communication in your 1st year of studying?
3. Did you have any trouble with passing your exams in your 1st year of studying?
4. Did you come across any adaptation difficulties in your 1st year of studying?
5. Did you have signs of severe stress in your 1st year of studying?
6. Have you asked yourself why you have entered the University?
7. Do you consider yourself an anxious and nervous person?
8. Did you have a wish to ask for help and (or) social support in case of difficulties in the 1st year of studying?
9. Do you think there should be a social and psychological service at the YSMU?
10. Do you need social and psychological aid?
11. Are there students who, in your opinion, require mental aid and (or) social support while studying at the University?

The level of interest in various social and psychological needs has been examined. Students were offered to select one of the following options such as 'yes', 'rather yes than no', 'no', 'rather no than yes'.

RESEAERCH RESULTS

It should be noted that 40.8% (352 people), 25.7% (222 people) and 32.6% (281 people) came across difficulties in learning, adaptation, had severe stress in the 1st year of studying, respectively; 25.6% (221 people) thought that their entry into the medical University was accidental. These students provided a positive answer ('yes') to these questions.

Percentage of students who rather agree with these questions is also significant. Their response was 'rather yes than no'. They included 32.1% (277 people), 26.1%

Table. The results of the survey of students concerning their interest in the formation and functioning of the social and psychological service.

Question	Yes	Rather yes than no	No	Rather no than yes
Did you have any difficulties in learning in your 1st year of studying? % (*n*)	40.8% (352 people)	32.1% (277 people)	21.2% (183 people)	5.9% (51 people)
Did you have any trouble with communication in your 1st year of studying? % (*n*)	14.0% (121 people)	13.3% (115 people)	30.7% (265 people)	41.9% (362 people)
Did you have any trouble with passing your exams in your 1st year of studying? % (*n*)	18.1% (156 people)	23.4% (202 people)	27.7% (239 people)	30.8% (266 people)
Did you come across any adaptation difficulties in your 1st year of studying? % (*n*)	25.7% (222 people)	26.1% (225 people)	24.0% (207 people)	24.2% (209 people)
Did you have signs of severe stress in your 1st year of studying? % (*n*)	32.6% (281 people)	19.4% (167 people)	21.5% (186 people)	26.5% (229 people)
Have you asked yourself why you have entered the University? % (*n*)	25.6% (221 people)	15.9% (137 people)	18.7% (161 people)	39.8% (344 people)
Do you consider yourself an anxious and nervous person? % (*n*)	22.7% (196 people)	25.8% (223 people)	23.3% (201 people)	28.2% (243 people)
Did you have a wish to ask for help and (or) social support in case of difficulties in the 1st year of studying? % (*n*)	19.7% (170 people)	12.3% (106 people)	15.5% (134 people)	52.5% (453 people)
Do you think there should be a social and psychological service at the YSMU? % (n)	56.0% (484 people)	32.7% (282 people)	5.7% (49 people)	5.6% (48 people)
Do you need social and psychological aid? % (*n*)	30.6% (264 people)	35.0% (302 people)	18.6% (161 people)	15.8% (136 people)
Are there students who, in your opinion, require mental aid and (or) social support while studying at the University? % (*n*)	62.6% o (540 people)	27.5% (237 people)	5.3% (46 people)	4.6% (40 people)

(225 people) and 19.4% (167 people) who had difficulties in learning, adaptation, and had severe stress in the 1st year of studying, respectively; 15.9% (137 people) thought that their entry into the medical University was accidental.

The conducted survey confirms that entry into the medical university and the first year of study are associated with the difficulties that occur while shifting to a new educational environment.

The survey has shown that 30.6% (264 people) believe that they require social and psychological aid, 35.0% (302 people) say it's 'rather yes than no'.

It should be noted that 62.6% (540 people) responded 'yes' and 27.5% (237 people) responded 'rather yes than no' when answering the question whether some students require psychological aid and (or) social support during their education at the University.

So, while answering the question whether a medical university should have a social and psychological service, 56.0% (484 people) believe that it's 'yes', 32.7% (282 people) think that it's 'rather yes than no'.

DISCUSSION OF RESULTS

Analysis of the survey results provided by the medical students has shown that the students are interested in the development of social and psychological aid and support. Adaptation of first-year students is particularly relevant, as studying in the first year is just adaptation to the conditions and organization of the educational process, development of independence, discipline, and communication skills (Table).

Thus, Center for Social and Psychological Support of Students has been organized in 2022–2023 at the Yaroslavl State Medical University to provide for urgent and direct support to the students who come across crisis and conflict situations, have social difficulties, difficulties in learning and mastering new material.

Basic objectives of the Center are to display cooperation in adaptation to educational activity of the first-year students and create conditions for positive socialization of the students.

As almost half of the students who participated in the survey (51%) mentioned mental problems and severe stress, provision of social and psychological consultation and complex social and psychological support to students was an important focus area for the Center. Its professionals provide timely psychological aid (psychological diagnostics and consultation) based on the students' requests, render social aid and support. Specialists from the Center pay significant attention to ethical issues, which is extremely important in the subsequent work of future medical students [7].

Psychological correction, development of positive communication skills and no-conflict behavior are aimed at creation of the favorable social and psychological environment and prevention of dismissal of students due to the social and psychological disadaptation.

Such basic problems as conflicts within a group, anxiety, and stress have been found among students, especially during exams, as well as domestic problems.

The problems are solved in basic diagnostic and awareness raising areas.

Individual counselling is provided at the students' requests within the first area. Specialists from the Center practice a person-centered approach, which is aimed at complete mental and personal development of a student. Diagnostic analysis is done, internal problems of a student are detected, health is estimated, and interaction with the environment is analyzed. Contact individual professional-student collaboration allows to define a priority (key) issue and decide how to deal with it.

Specialists of the Center provided practical aid in case of difficulties in learning and while building interpersonal relations within a group, while having psychological problems, in anxiety and negative emotional conditions, conflicts within a family and a group.

The need in the formation of social and psychological service at the University is confirmed by the obtained results. The students who were on the verge of expulsion changed their attitude to the educational process, were motivated for the subsequent study at a medical University, and none of the involved students were expelled.

Awareness raising work of the Center includes various forms of working in groups. It means organization of conferences, round tables, master classes in social and psychological support of students. Subsequent development requires training in communication, group cohesion, self-determination, development of leadership, tolerance, etc.

CONCLUSIONS

Thus, educational quality of medical students depends on their social and psychological well-being. So, formation of the social and psychological support service at a higher educational institution is considered as an essential part of the educational process. Need in this aid is confirmed by the survey data. Provision of practical aid to students, social and mental health support, prevention of social disadaptation belong to the main challenges. They are solved in participation of specialists from the Center of Social and Psychological Support of the YSMU.

Close cooperation with the training department and the entire pedagogical group will enable to decide the basic objective faced by the medical university and associated with the provision of modern qualitative medical, pharmaceutical, psychological and social education.

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PREGNANT WOMEN AND THEIR FETUSES — ORPHAN POPULATIONS IN RESPECT TO THE SAFETY AND EFFICACY OF MEDICINES

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Pregnant women are a very special category of patients. The risk-benefit ratio of using various drugs in this case presents a significant medical, social and ethical problem. The increase in the age of onset of the first pregnancy is associated with the increasing prevalence of chronic pathology. Obesity, cardiovascular diseases, diabetes mellitus, hypo- or hyperfunction of the thyroid gland, as well as many other conditions contribute to the active use of drugs of various pharmacological groups throughout the entire period of pregnancy, including early periods. The current practice of pharmacotherapy in pregnant women is based mainly on the use of drugs with an uncertain teratogenic risk. Not including pregnant women in clinical trials is an ethical issue as significant as their potential inclusion. Previously, for a long time, vulnerable categories included generally all women of reproductive age, whose inclusion in clinical trials became possible only in the mid-1990s. Pregnant women were considered vulnerable until 2019. The orphan status of pregnant women in terms of inclusion in clinical trials limits their right to receive highly effective and safe medical care, which makes it relevant to review the existing ethical principles in relation to this category of patients and a to perform a detailed analysis of existing barriers for certain types of drug trials.

Keywords: pregnant women, clinical trials, vulnerable categories of patients, efficacy and safety of pharmacotherapy

Author contribution: Ushkalova E. A. — literature analysis, collection, analysis and writing the publication text; Zyryanov S. K.— trial planning, literature analysis; Butranova O. I.— data analysis and interpretation.

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БЕРЕМЕННЫЕ ЖЕНЩИНЫ И ИХ ПЛОДЫ — ОРФАННЫЕ ГРУППЫ НАСЕЛЕНИЯ В ОТНОШЕНИИ БЕЗОПАСНОСТИ И ЭФФЕКТИВНОСТИ ЛЕКАРСТВЕННЫХ СРЕДСТВ

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Беременные женщины представляют собой совершенно особую категорию пациентов. Соотношение рисков и пользы применения различных лекарственных препаратов представляет в данном случае значимую медицинскую, социальную и этическую проблему. Увеличение возраста наступления первой беременности связано со все более широким распространением хронической патологии. Ожирение, сердечно-сосудистые заболевания, сахарный диабет, гипо- либо гиперфункция щитовидной железы, а также многие другие состояния способствуют активному применению препаратов различных фармакологических групп на протяжении всего периода беременности, включая ранние сроки. Существующая практика фармакотерапии беременных основывается преимущественно на применении препаратов с неопределенным тератогенным риском. Невключение беременных в клинические исследования является этической проблемой столь же значимой, как и их потенциальное включение. Ранее, в течение длительного времени, к уязвимым категориям относили в целом всех женщин репродуктивного возраста, чье включение в клинические исследования стало возможным лишь в середине 1990-х. Беременные женщины рассматривались в качестве уязвимых вплоть до 2019 г. Орфанный, с точки зрения включения в клинические исследования, статус беременных ограничивает их право на получение высокоэффективной и безопасной медицинской помощи, что делает актуальным пересмотр существующих этических принципов в отношении данной категории пациентов и детального анализа существующих барьеров для осуществления определенных видов исследований лекарственных препаратов.

Ключевые слова: беременные, клинические исследования, уязвимые категории пациентов, эффективность и безопасность фармакотерапии

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Despite all the advances in modern medicine, health of pregnant women is not improved, but even gets worse. Thus, the U.S. has experienced a rise in severe maternal morbidity and mortality for more than twice over the last 3 decades. This is partially explained by the aging of pregnant women and an increase in the prevalence of chronic diseases and obesity among them [1]. Obesity and maternal age above 35 and especially above 45 contribute to a wide specter of unfavorable outcomes of pregnancies, including intrauterine growth restriction, congenital abnormalities, higher risk of miscarriages, premature births, stillbirths, Caesarean sections, preeclampsia, pregnancy diabetes and other complications [2,3]. This risk is increased even more when a pregnant woman has concomitant diseases/conditions, including hypertensive disturbances and pregnancy diabetes [4]. Among women with multiple chronic conditions, deliveries have 3.8 times the rate of severe maternal morbidity and mortality compared to women without chronic conditions [1]. Out of 210 million annually

recorded pregnancies, an estimated 140 million only result in a live birth per year [5].

Women with chronic diseases not treated during the gestational period are at increased risk of postpartum complications, including cardiometabolic, renal [4,6] and mental ones [7]. In the U.S., cardiovascular diseases are responsible for 26% of pregnancy-related mortality during the first year postpartum [1]. In the perinatal period, suicide is committed by every 25th woman aged 20 to 35 [8], during the first year postpartum it is the reason for 20% of maternal mortality [9]. In depressive postpartum psychosis, the rate of infanticide is 4.5% [10].

Thus, many pregnant women with chronic diseases require pharmacotherapy throughout the entire period of pregnancy, including organogenesis associated with the risk of teratogenic effects. Moreover, pregnant women need drugs to treat acute diseases, including life-threatening ones, and obstetric disorders, and in some cases to prevent and treat fetal diseases. However, it is not always possible to compare the risk associated with a not treated disease and the risk related to the use of pharmacotherapy due to insufficient research of effectiveness and safety of drugs during gestation. Despite pharmacotherapy is obtained by at least 80–90% of pregnant women [11], data about effectiveness and safety of more than 90% of MPs present in the market in the period of gestation are not sufficient [12,13]. Data concerning pharmacokinetics and effectiveness of drugs among pregnant women are predominantly extrapolated from animal experiments or studies involving non-pregnant women and men, who still represent the majority in clinical trials. Fetal safety information is based on results of trials involving pregnant women in 5.2% of cases only; in other cases, it is obtained during animal experiments [13], though species sensitivity to the teratogenic effects was shown as early as the middle of the last century when thalidomide use was investigated. In this regard, almost all drugs that enter the market have an 'indefinite' teratogenic risk, whereas the interval required to select a more exact risk category is 27 years in average [14].

The majority of medicines are not officially approved for use during pregnancy. They are used off-label in doses and dosage regimens intended for non-pregnant women. At the same time, significant physiological changes in pregnancy induce alterations to all pharmacokinetic properties of medications. Development of new organs, such as placenta, uteroplacental blood flow and fetus, leads to significantly altered distribution, metabolism and excretion of various drugs. At the same time, maternal, fetal and placental activity of enzymes and transporters is dependent on gestational age. Dose adjustment can be required in various trimesters [15], whereas activity of some of them is subjected to genetic polymorphism [16]. During drugs biotransformation, novel metabolites not common for non-pregnant women can be formed in the placenta, including epoxides with teratogenic potential [15].

Thus, the ratio of risks and benefits of using various drugs in pregnant women remains unknown. It requires an urgent solution [17].

ETHICAL ISSUES OF STUDYING EFFECTIVENESS AND SAFETY OF MEDICINAL PREPARATIONS DURING PREGNANCY

Pregnant women are reluctant to be included in pre-marketing clinical trials and — in 95% of cases — in Phase IV clinical trials, where drugs are investigated in case of commonly occurring gestational conditions [18]. To a large extent, the reasons for these exclusions might be due to the two tragedies of the middle of the last century. Thalidomide used in 1957–1961 led to 8000–12000 children being born without limbs and with other birth defects, whereas diethylstilbestrol prescribed in the 1970s resulted in vaginal adenocarcinoma among women who were exposed to this preparation in utero.

In 1977, the FDA issued a guideline to exclude women of child-bearing age from Phase I and Phase II clinical trials, whereas pharmaceutical companies and research communities applied the exclusion to Phase III and Phase IV trials [14]. In 1979, the vulnerability concept has held a central place in research ethics guidance [19, 20]. Despite there is no unambiguous definition of the term and persons related to the category in scientific literature, it means that additional protection in clinical research is required and participation of vulnerable patients is restricted [21].

For a long time, vulnerable categories included generally all women of reproductive age, whose inclusion in clinical trials became possible only in the mid-1990s, when adequate safety measures have been followed (pregnancy testing, adequate contraception). Women who became pregnant during clinical trials were excluded. Pregnant women were considered vulnerable until 2019. So, the women and their fetuses have received the orphan status in terms of drug safety and effectiveness [22].

Meanwhile, concept analysis of women's vulnerability during pregnancy has shown that the patients are vulnerable only because in real medical practice they are increasingly under the growing risk of unfavorable effect due to limited science knowledge [23].

Owing to the lack of evidence data, the dose for pregnant women is equal to that obtained by non-pregnant women and men, which can result both in excessive blood concentrations or toxic effects, and insufficient concentrations that make therapy ineffective [17]. It puts the health and life of millions pregnant women and their fetuses/children at risk and raises the question of whether it is 'justifiable to include' pregnant women into randomized clinical trials (RCT) [21, 24].

Exclusion of pregnant women from the RCT violates fundamental principles of medical ethics, including the 'First Do No Harm' part of the Hippocratic Oath. It also violates the principle of respect for patient autonomy, which means that patients take an independent and informed decision about necessary methods of diagnostics and treatment, and the principle of justice, as it results in ignoring specific medical needs for this group of patients and slows down the affordability of the latest medical achievements [25]. The American College of Obstetrics and Gynecology (ACOG) suggests that pregnant women should be defined as 'scientifically complex' rather than a 'vulnerable' population. It means that a more frequent and targeted monitoring is required during the research [17]. The approach allows pregnant women to take an ethical decision for themselves and their fetuses [25].

CHALLENGES IN CONDUCTING CLINICAL RESEARCH INVOLVING PREGNANT WOMEN

Clinical research with participation of pregnant women can limit a number of factors on the part of drugs manufacturers, regulatory authorities and pregnant women themselves [11]. For manufacturers, such limiting factors include the risk of intense battles with the courts in case of unfavorable treatment outcomes, even if they weren't attributed to this exact drug; insignificant drug market size during pregnancy, and duration of use, which is pregnancy-limited in many cases. This can fail to

justify the costs for the drug registration and related regulatory burden [17]. Another limiting factor includes off-label use of medications: in real clinical practice pregnant women obtain drugs officially not approved for use during the gestational period. This is how a pharmaceutical company obtains financial income without being exposed to forensic risk.

Regulatory authorities also bear certain responsibility for the lack of adequate information on the use of drugs during pregnancy, as they do not require participation of pregnant women in clinical research during drugs registration and consider them vulnerable. Moreover, the research requires independent funding, which allows the regulatory authorities not to depend on manufacturers' drug registration fees [26].

It is frequently seen that pregnant women refuse to participate in research of novel drugs as they fear of the potential fetal risk, especially when there is no benefit for the women themselves (in the presence of alternative drugs to treat the pathology). Participation of pregnant women in pharmacokinetic research limits its duration. Thus, if an investigated drug has to be administered twice a day, a woman shall stay at the research center for 12 hours; ideally, the research should be conducted every trimester and in the postpartum period, which is even more complicated for breastfeeding women.

Another challenge is that clinical research involving pregnant women requires long-term follow-up to adequately assess not just outcomes for fetuses and newborns, but also potential effects on health and behavior of children [11].

Despite the abovementioned challenges, practicing physicians, researchers, professional communities and regulatory authorities are aware of the need in adequate clinical research of drugs during pregnancy [25]. In 2018, FDA and other American organizations engaged in development and control of drugs submitted a draft guidance for manufacturers that should be taken into account for scientific and ethical reasons while including pregnant women in clinical research [27]. To stimulate clinical research among pregnant women, it is recommended to use the experience of pediatric randomized clinical trials, which has resulted in significant progress within the last 15–20 years [11]. Thus, it is time to cancel the orphan status of pregnant women and their fetuses and allow mothers to exercise their ethical right to adequate medical aid, including the right for rational pharmacotherapy adjusted for the needs of this category of patients.

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ETHICAL ISSUES OF THE THERAPY OF PREMATURE INFANTS

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Currently preterm births are the leading causes of newborn mortality in developed countries. There is growing concern in the medical community about the moral and ethical implications of therapeutic care for these patients. The article raises the problem of joint decision-making by neonatologists and parents on the treatment of premature newborns. Including the question of who is most qualified to make decisions regarding the initiation, termination or withdrawal of life-sustaining treatment for preterm infants. The rest of the life of surviving premature newborns may be associated with inconvenience and suffering in everyday life, and understanding of responsibility for the life of the patient and the child greatly complicates the decision. Another important issue is the relationship between intensive care nurses and parents in caring for premature newborns. The article describes the life experience and ethical and moral problems that medical personnel face during caring for premature newborns.

Keywords: premature infants, neonatologists, paternalism, intensive care

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ЭТИЧЕСКИЕ АСПЕКТЫ ТЕРАПИИ НЕДОНОШЕННЫХ НОВОРОЖДЕННЫХ

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В настоящее время преждевременные роды являются основной причиной смертности новорожденных в развитых странах. В медицинском сообществе растет озабоченность по поводу моральных и этических последствий терапевтической помощи данным пациентам. В статье поднимается проблема о совместном принятии решений врачей-неонатологов и родителей о проведении терапии недоношенным новорожденным. В том числе и вопрос о том, кто имеет наибольшую квалификацию, чтобы принимать решения в отношении инициирования, прекращения или отказа от поддерживающего жизнь лечения недоношенных новорожденных. Дальнейшая жизнь выживших недоношенных новорожденных может быть связана с неудобствами и страданиями в повседневной жизни, а понимание ответственности за жизнь пациента и ребенка значительно затрудняет принятие решения. Важным также является вопрос об отношениях между медицинскими сестрами отделений интенсивной терапии и родителями при уходе за недоношенными новорожденными. В статье описывается жизненный опыт и этические и моральные проблемы, с которыми сталкивается медицинский персонал при выхаживании недоношенных новорожденных.

Ключевые слова: недоношенные новорожденные, врачи-неонатологи, патернализм, интенсивная терапия

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According to the Ministry of Health, over 100 thousand preterm neonates are born in Russia annually. Survival of this group of patients is 97% [1]. Despite that, preterm birth is the main reason for neonatal mortality (during the first 4 weeks of life) in developed countries. In Russia, they nurse neonates who were born at 22 weeks and have a body mass of over 500 g and body length of over 25 cm as per standards established by the World Health Organization [2].

In Russia, the rate of preterm birth is about 6%. In Europe and the U.S., it is slightly higher and constitutes 10–13%. This is due to widespread introduction of novel assisted reproductive technologies, higher number of multiple births, expanded indications for preterm birth, and growing number of single premature deliveries, when birth is either induced or when Caesarean section is performed [3]. Maternal concomitant diseases (gestational diabetes, hypertension and diabetes) and a lack of qualitative perinatal care required to support full-term pregnancy produce a large effect on preterm birth.

Very early preterm labor (22–27 weeks), early preterm labor (28–30 weeks), preterm labor (31–33 weeks) and late preterm labor (34–36 weeks) are differentiated taking into account gestational age [4]. Prematurity is determined based on neonatal body weight: up to 1,000 g for extremely low body weight (ELBW); 1,001 to 1,500 g for very low body weight (VLBW); and 1,501 to 2,500 g for low body weight (LBW) [4]. Modern medicine has made remarkable clinical and technical progress, which would allow an unprecedented increase of survival rates among premature children. The current viability threshold depends on the physiological development of the lungs, which occurs approximately at gestational weeks 22–24 [5]. Unfortunately, infants with the lowest threshold still have no

absolute survival rates, whereas some of those who survive can have severe disorders and disabilities.

In Russia, current survival of children with body mass of less than 1,000 g is 85%, the number reaches 90% in perinatal centers [1]. There is an opinion that this was facilitated by experimental methods of treatment without ethically approved clinical trials or without informed consent of parents or legal representatives. But if those prematurely born survived in 100% of cases and if intensive therapy did not produce physical, mental or cognitive adverse effects or complications, this area of medicine would fail to be developed. However, there exist numerous short-term and long-term issues, which should be taken into account prior to intensive care of neonates with ELBW and LBW or its withdrawal.

Despite dramatic improvement of fetal mortality rates during the last decades, premature neonates belong to the group of high risk of infectious complications, including respiratory distress-syndrome, bronchopulmonary dysplasia, apnea, necrotizing enterocolitis, patent ductus arteriosus and anemia of prematurity [6]. Immature immune system increases a risk of pneumonia, sepsis, meningitis and urinary tract infections to protect from viruses, bacteria and other pathogens [7].

Thus, neonatologists believe that intensive therapy is an essential condition of survival of neonates with ELBW and LBW with gestational age of less than 29 weeks. Nevertheless, a doctor can't warrant full recovery of these patients only because the neonates can survive. Interruption and withdrawal of intensive treatment for neonates should be discussed not by neonatologists only, but also by parents or legal representatives, rehabilitologists, other pediatricians and representatives of the community.

There is growing concern about moral and ethical consequences of complex and technological aid provided to children with ELBW at neonatal intensive care units in developed countries [5,7]. Nurses who take care of seriously ill patients stay at the bedside daily, and foster neonates with severe complications that require complex and frequently painful treatment.

They have to communicate with families, who are often upset and depressed because of the condition of their neonates, and come across ethical and moral problems daily while taking care of premature neonates with ELBW and LBW [3]. Despite this, daily 'live' experience of perception by nurses of their collision with various moral and ethical dilemmas receives minimal attention and is described in a small number of articles [5,7].

The nurses participating in the trial by *Webb S.* openly discussed their experience of solving moral and ethical issues they came across. They reported that they often had troubles with their moral sense, especially when they unconsciously tried to protect neonates from pain and unnecessary discomfort. Despite moral and ethical issues, the nurses still remained loyal to what they did. According to the results, the participants had to deal with ethical principles such as beneficence, non-harm, social justice and parents' autonomy. Decisions taken by parents of neonates could possibly be the most complex problem faced by nurses of an intensive care unit. Some participants announced that families were not always properly informed by neonatologists of a very bad prognosis for therapy outcomes and had hopes for impossible wonder. According to a nurse, parents were asked to take decisions they were not capable of. It is especially difficult for parents to take decisions due to such factors as incapacity to foresee a long-term prognosis and outcomes, young age and minimal death-related experience, as they always hoped for wonder and were in stress when the child was hospitalized.

One of the most important issues was remote treatment outcomes that influenced a patient's quality of life. For instance, the issue of whether premature children can complete primary school and take care of themselves in the future. Unlike the majority of neonatologists and nurses, the major part of the population considers the issues central while discussing the need to provide intensive therapy to premature neonates [8]. It is most frequently associated with the need for life support by parents and society. Parents should also take into account how children with possible cognitive or physical disturbances can influence the family life and other children.

Some healthcare representatives believe themselves to be the best alternative to protect and take decisions on behalf of a preterm newborn [8]. Neonatologist-newborn relationship is definitely paternalism (doctor-patient relationship when a patient totally relies on qualification and experience of a treating physician). But is this pure paternalism? Does a doctor have a scientific interest while taking decisions on conflicting issues? That's why neonatologists and nurses have to take joint decisions about intensive therapy with parents or legal representatives.

According to a modern study by Fauchère et al, it is assumed that a paternalistic attitude can mean that neonatologists do not supply parents with complete information about their premature newborn's condition just not to disturb them. However, there is a risk that it is done to exclude parents from taking decisions.

But what would doctors tell parents? Will they inform of various risks of health worsening [9]? Will they inform of the autism risk due to long-term treatment in couveuse [10]? How would they submit the data? Will they exaggerate the expected favorable outcome [11]? According to Fauchère et al., doctors who take part in participation could have their own personal values. They also state that cultural values could influence the attitude towards patients and indicate at various results in the involved German- and French-speaking countries. The differences could have an influence on whether the intensive therapy was initiated, suspended or withheld. The differences were registered in other researches as well [6,11,12].

The study discusses whether premature children with ELBW should be treated with other neonates and elder children. Significantly more doctors (82%) than nurses (57%) announced that the same ethical principles should be applied. However, replies to the questions can't be definitive as we don't know how those interviewed raised the issue. If we understand the principle, according to which equal cases should be considered equally, and if the need should determine our actions, it is easily to agree that premature children with ELBW and LBW should be treated just like other children are. The age itself means nothing for prioritization.

Tolerability of certain therapy in various patients of the same age with similar diagnosis should be taken into account. Patient A can have a much better treatment outcome than Patient B who is very weak, has several concomitant diseases and can fail to survive a potential surgery. In this case, if a doctor decides that the surgery can do more harm than benefit to patient B, we should not carry out the procedure. So, equal cases are not always really equal due to concomitant medical differences. Thus, equal attitude is not always possible.

If we apply the judgement to intensive therapy of premature neonates with ELBW and LBW and compare it with therapy obtained by neonates or children, significant differences will be registered. If the prognosis is very pessimistic in relation to survival and quality of life of premature infants, the doctors can refuse from life-sustaining therapy.

The study by Fauchère et al. has shown that nurses were less willing to use too aggressive treatment as compared to neonatologists. It could be because they felt that this could not be in the best interests of the patients. It is noted in the study that parents or legal representatives should participate in taking decisions though doctors and nurses can have different views on the therapy course. The parents' interests are applied to the entire family and go beyond intensive therapy obtained by their premature infant.

Doctors can neglect the use of a family-oriented approach in such cases. Nevertheless, discussion of ideas, hopes and preferences of families preceded by informing parents of what their child can come across in the future should be an important step in the process of common decision-making. Family care is an essential condition to submit adequate data and promote sincere joint participation in taking decisions. Doctors and nurses in the intensive care units should follow the family-oriented models when they inform parents or legal representatives of potential treatment outcomes for premature neonates with ELBW and LBW. Joint evidence-based decision should be made without a paternalistic effect and effect of personal values of neonatologists. Families and legal representatives should be well-informed and obtain data in an honest but clear way, as this is important for taking joint decisions.

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ETHICAL ISSUES OF PHARMACOTHERAPY AND CLINICAL TRIALS IN PATIENTS WITH DEMENTIA

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Dementia raises many ethical issues associated with stages of dementia such as the appearance of preclinical and asymptomatic patients who are, however, at risk of dementia. Thus, physicians come across ethical issues about preventive measures, disclosure of risks and protection from stigmatization and discrimination. Despite efforts to prevent dementia, it is also necessary to solve ethical issues related to the study of ways to alleviate the symptoms of clinical dementia, with the need for additional protection of patients with dementia when prescribing pharmacotherapy. One of the possible ways to solve these issues should be to use an integrated approach to conducting clinical trials and analyzing the ethical, legal and social consequences of dementia, for which it is necessary to include the collection of ethics-related data in the design of the dementia study itself.

Keywords: dementia, ethics, pharmacotherapy, clinical trials

Author contribution: Zyryanov SK — article designing, scientific counselling, literature counselling; Kazakov AS — review of article-related publications, writing an abstract, writing an article.

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ЭТИЧЕСКИЕ ПРОБЛЕМЫ ПРОВЕДЕНИЯ ФАРМАКОТЕРАПИИ И КЛИНИЧЕСКИХ ИССЛЕДОВАНИЙ У ПАЦИЕНТОВ С ДЕМЕНЦИЕЙ

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Деменция поднимает много этических проблем, связанных со стадиями прогрессирования деменции, таких, как появление доклинических и бессимптомных, но подверженных риску развития деменции категорий пациентов, что ставит перед лечащими врачами этические вопросы о профилактических мерах, раскрытии рисков и защите от стигматизации и дискриминации. Несмотря на усилия по профилактике деменции, также приходится решать этические проблемы, связанные с изучением способов облегчения симптоматики клинической деменции, с необходимостью дополнительной защиты пациентов с деменцией при назначении фармакотерапии. Одним из возможных способов решения данных проблем должно быть использование комплексного подхода к проведению клинических исследований и анализу этических, правовых и социальных последствий деменции, для чего необходимо включать сбор данных, связанных с этикой, в дизайн самого исследования деменции.

Ключевые слова: деменция, этика, фармакотерапия, клинические исследования

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Progressively diminishing decisional capacity of patients, dementia raises ethical issues, which vary as the disease progresses from early biomarkers in the blood that predict the risk of dementia to early clinical symptoms and more severe stages.

Discovery of biomarkers associated with pathophysiology of Alzheimer's disease and other neurogenerative disorders transformed the way how the disorders were detected and diagnosed, and changed the contours of ethical issues faced by both healthcare professionals, and patients. According to available scientific data, pathophysiology of Alzheimer's disease, which is the most common cause of dementia, begins long before a person becomes a patient with observed signs and symptoms of dementia [1]. During another trial, a group of patients with 'asymptomatic risk of Alzheimer's disease' is revealed, and the role of biomarkers in determining the stage of the disease is confirmed [2]. Thus, detecting biomarkers based on genetic testing or cerebrospinal fluid analysis at the preclinical and symptomless stage of the disease raises a number of complex ethical issues associated with pharmacotherapy of patients with dementia.

First, what are the ethical consequences of shifting the focus of medical research from studying pharmacotherapy approaches in patients with symptomatic Alzheimer's disease to examining the same (including preventive pharmacotherapy) in symptom-free patients with a risk based on biomarkers? Second, how can we protect patients with a high risk of dementia from stigmatization and discrimination that accompany the majority of forms of irreversible cognitive impairment? The third ethical issue arising at this stage is as follows: what is the clinical and social benefit from knowing the risk status if developing effective methods of treatment of Alzheimer's disease and other dementias has proved difficult?

Several large clinical trials related to secondary prevention of Alzheimer's disease and other dementias and also preventing

cognitive impairment among persons with already manifested signs of dementia have been conducted [3–5]. The clinical trials were conducted because other clinical trials that investigated approaches to pharmacotherapy in patients with symptomatic forms of dementia (for instance, pharmacological substances aimed at beta-amyloid) failed to slow the progression of dementia. The obtained negative findings of the conducted trials resulted in new trials with involvement of patients without noticeable symptoms of memory loss but with biomarker-based risk factors. The purpose of the trials is that the beginning of pharmacotherapy prior to neurodegeneration can be more effective than that among patients who have already lost a part of neurons.

Clinical trials aimed to prevent the development and progression of dementia raise three ethical issues. First and most importantly, in some clinical trials participants get to know their risk factors for dementia, as the risk is an inclusion criterion for the trial [4]. The ethical issue means that the trials aimed to prevent development and progression of dementia require thorough development of algorithms and procedures to reduce harm, which can accompany disclosure of data about the risk of dementia. Second, some participants of clinical trials aimed at prevention and progression of dementia could probably never shift from a biomarker-based positive status (entitling to be included into a trial) to clinical symptoms. As a result, the risk represented by the clinical trials for the subgroup with positive biomarkers, which would never progress to clinical dementia, should be included into the total risk-benefit ratio of the conducted trial. Third, the clinical trials aimed to prevent the development and progression of dementia have, on the one hand, an ethical advantage, as they involve persons whose cognitive capabilities allow to weigh the risks and benefit [4]. On the other hand, it means that the clinical trial participant is made totally responsible for the independent dealing with complex ethical issues arising during the trials (such as disclosure of biomarker status, assessment of preventive pharmacotherapy benefit and harm, etc.).

As risk ethics issues focus on the possible development of dementia in cognitively normal subjects or patients with indistinct symptoms, dementia resulting in significant cognitive impairment is developed in some of them. Progression of cognitive impairment raises a number of other ethical issues. They are about how to achieve a balance between the possible benefit of pharmacotherapy aimed at reduced dementia symptoms and protection of the group of patients from possible risks associated with increased vulnerability.

Since 1950, numerous national and international codes such as the Declaration of Helsinki establish guidelines regulating clinical trials, including their independent inspection, risk-benefit ratio for potential participants, so that the vulnerable groups of population are not the objects of trials at risk [6]. Several ethical issues arise here as well. First, if it is assumed that respect for the identity means that people can take their own decisions about participation in clinical trials, how can decision-making ability and competence among people with dementia be determined and assessed?

Second, if a patient with dementia is not competent enough to consent to the trial, can the legal representative provide consent instead of the patient from an ethical perspective and to which type of the trial? The issues are still important even today. Though a number of trials aimed at development and progression of dementia is increased, various clinical trials involving persons with clinically pronounced dementia whose cognitive impairment cause complex ethical issues concerning obtaining consent to participation are being continued as well.

A doctor decides which patients with dementia can consent to medical procedures or participation in a clinical trial based on the human abilities to take decisions such as comprehension (ability to think over a respective situation), assessing the situation (ability to apply the data to own situation), speculation (ability to compare the suggested options and conclude about potential consequences of choice) and uttering a choice (ability to report the taken decision) [7]. Estimating the four abilities, the doctor concludes whether the person can take a respective decision about subsequent therapy or participation in a clinical trial [8].

Trials examining the abilities of patients with dementia to take decisions independently show that the probability of being classified as those capable of taking independent decisions depends not only on total severity of cognitive impairment, but also on the risks of suggested pharmacotherapy or a clinical trial: the risky the drug-induced intervention is and the more severe manifestations of dementia the patient has, the more likely it is that the patient will be treated as incapable of taking decisions [8,9].

Nevertheless, some trials show that in case of many neurological and psychiatric diseases a corresponding diagnosis does not make a person legally incapable [9,10]. Diagnostics of Alzheimer's disease or another dementia should also not be perceived as the determining factor for human incapacity. Over a half of patients with a very mild form of Alzheimer's disease can provide an informed consent to medical procedures, whereas the majority of (but not all) patients with a moderate form of the disease are not capable of giving the same consent [8,11]. These and other trials show that mild and moderate forms of Alzheimer's disease can't be automatically interpreted as an inability to provide an independent informed consent to suggested pharmacotherapy or participation in a clinical trial [12,13].

Thus, research of an ability of patients with dementia to take decisions about treatment results in three key conclusions with respective ethical consequences. First, patients with mild and early moderate forms of Alzheimer's disease should not be treated as those who are incompetent in making decisions about clinical treatment. It is so because some patients, and those who better understand their condition and have mild dementia, in particular, are competent in taking decisions about treatment. Second, at a certain point the competence is evidently lost. It means that early diagnostics and disclosure of diagnostic data are essential, as then the patients can report their preferences in treatment beforehand. Third, patients want to participate in taking treatment-related decisions insofar as their abilities permit, mentioning importance of the patients' involvement even if this doesn't allow them to take a final decision about treatment. A possible perspective trend in solving various ethical issues that occur during drug-induced therapy of dementia includes an integrated approach to conducting clinical trials and analyzing the ethical, legal and social consequences of dementia, for which it is necessary to include the collection of ethics-related data in the design of the dementia study itself. The integration can be helpful while solving many ethical issues, including when trying to find a balance between potential advantages of early interventions and potential harm of stigmatization and discrimination.

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ETHICAL ISSUES IN PEDIATRIC CLINICAL TRIALS

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Historically, instead of conducting well-designed research studies in the pediatric population, drug monographs indicate that safety and efficacy in children have not been evaluated. Among the main challenges in clinical trials for children, ethical issues occupy a special place, as they arise at almost all stages — from clinical trials to extrapolation. In the article, the authors present the history of clinical research in pediatrics and neonatology, how the view of involving children in clinical trials has changed, the specific ethical problems of children's participation in clinical trials, legislative initiatives and other agreed measures taken and what they have led to. The ethical issues of microdosing in pediatrics, methods for the first-in-pediatric dose selection, issues of acceptability and drug development for the treatment of rare diseases are discussed separately. Conducting trials in the most vulnerable pediatric groups — newborns and premature newborns — is presented in detail. The potential reasons for trial failures in children are presented with specific examples.

Keywords: children, ethics, clinical trials, drugs

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ЭТИЧЕСКИЕ ПРОБЛЕМЫ ПРИ ИЗУЧЕНИИ ЛЕКАРСТВЕННЫХ СРЕДСТВ В ПЕДИАТРИИ

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Исторически сложилось так, что вместо проведения хорошо спланированных исследований в детской популяции, в монографиях к лекарствам пишут, что безопасность и эффективность у детей не оценивали. Среди основных препятствий к изучению лекарств у детей вопросы этики занимают особое место, так как они возникают почти на всех этапах — от клинических исследований до экстраполяции. В статье авторы представляют историю клинических исследований в педиатрии и неонатологии, эволюцию взгляда на вовлечение детей в испытания лекарственных средств, конкретные этические проблемы участия детей в клинических исследованиях, а также законодательные инициативы и другие предпринятые согласованные меры и к чему они привели. Отдельно обсуждаются этические вопросы микродозирования в педиатрии, подходы, применяющиеся для определения первой педиатрической дозы, проблемы приемлемости и пути их решения, основные принципы разработки лекарственных средств для лечения редких заболеваний. Подробно рассматривается проведение испытаний в наиболее уязвимых педиатрических группах — новорожденных и недоношенных. Представлены вероятные причины неудач в ходе проведения клинических исследований у детей с приведением конкретных примеров.

Ключевые слова: дети, этика, клинические исследования, лекарственные средства

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RELEVANCE

Historically, many drugs, widely applied in pediatric practice, have not been properly studied in children. The drugs often lack complete data on safety, effectiveness and dosage in children, and, thus, the consequences of their prescribing are not known fully. As a rule, pediatricians are well aware of the lack of information about the use of the drug in children in many information leaflets. In this case, ethical, legal, economical and other considerations can result in refusal from potentially important drug-induced pediatric treatment with these drugs.

Another option available to a healthcare professional consists in using both unlicensed (not registered in pediatrics) and off-label (other than as intended) drugs [1]. As it was mentioned above, ethical aspects belong to one of the reasons of limited study of drugs. It should be noted that ethical issues arise almost at any stage of studying drugs in children, from clinical trials (CT) including pilot studies (study of microdosing, study of one dose at subtherapeutic doses or within the assumed therapeutic range, study of multiple doses), to extrapolation.

History of clinical trials in children

In the beginning of 1960, the world has faced significant changes in regulation of drugs. The thalidomide tragedy was the reason [2, 3]. This resulted in Kefauver-Harris amendments to the U. S. Food and Drug Act in 1962, and formation of national systems of spontaneous reports about adverse events. The positive effect of introducing the reporting system consists in additional control of drug safety. However, the changes designed to ensure a safer drug-induced pediatric therapy had an opposite effect as well [4]. Thus, according to Kefauver-Harris amendments, to obtain an approval for entering

the pharmaceutical market, a drug should be both safe, and have significant advantages over other drugs. The evidence should be presented to the Food and Drug Administration (FDA) for review.

The unintended consequence of the act taken in good faith is described the best by Shirkey H, a founder of pediatric pharmacology, in 1968. He used a term 'therapeutic orphans' to describe the existing situation when the majority of drugs presented in the market are not labelled as 'for use in children' though the drugs are actually widely used among children as first-line therapy [5].

Until 1997, the world has seen a few studies on development of drugs in pediatrics. Thus, data on proper dosing, safety and effectiveness, that could be used while prescribing the majority of drugs to children, were lacking for decades. Serious consequences of prescribing off-label drugs in children and slow acceptance of children by the society as participants of clinical trials paved the way for legislative initiatives in the U.S. and Europe [6]. Thus, the Food and Drug Administration Modernization Act was adopted in the U.S. indicating that a manufacturer or holder of a marketing authorization can get additional 6 months of exclusive sale of its product if there is an official request from the FDA to conduct pediatric studies [7].

From the clinical and scientific point of view, advantages of this act include a systemic mechanism for pediatric studies of novel drugs, establishment of effectiveness, safety and pharmacokinetic basis for use and dosing among children (from premature children to adolescents), and an incentive to search for the best ways for such trials.

Moreover, to overcome the shortage of drugs for pediatric use, coordinated efforts have been taken during the last 20 years, including development of national and international research networks for pediatric trials, and changes in the process of drug approval by regulating authorities. The taken measures promoted not only expansion of knowledge about the approved drugs but also urged manufacturing companies to include children into clinical trials of drugs that can be used in pediatrics in the future.

The Best Pharmaceuticals for Children Act, BPCA, adopted in 2002, and the Pediatric Research Equity Act, PREA, subsequently adopted in 2003, can serve as examples. Both BPCA, and PREA were updated in 2007 in accordance with the FDA Amendments Act, and became an essential part of the FDA Safety and Innovation Act in 2012. The Regulation on Medicines for Pediatric Use is a European equivalent of the act. The regulating authorities on both sides of the Atlantic have a right to request from the companies that submit applications for new drugs to present a detailed plan of the trial (Pediatric Study Plan in the U.S., Pediatric Investigation Plan in Europe) for the drugs that can be used in children [8]. Subsequently, over 1,200 pediatric trials were submitted to the FDA, with the majority of them being submitted since 2007. The 21st Century Cures Act, adopted in the U.S. in December 2016, accelerates development of novel medical products and contains some provisions that expand the ability to upgrade the plans of clinical trials and assessment of clinical outcomes, making the process of drug approval easier [7].

The Last Reauthorization FDA Act of 2017 expands the programs of the Best Pharmaceuticals for Children Act related to the trials of unpatented pediatric drugs until 2022 [9]. On the one hand, these changes create problems for drug manufacturers. This occurs because historically, inclusion of children into clinical trials was not a part of planning of drug development. It was difficult to perform so due to a number of reasons including ethical issues and issues associated with acceptability, rare occurrence, standardization, endpoints, safety, dosing and feasibility.

On the other hand, innovative developments such as new design of clinical trials, in silico pharmacology (pharmacometrics modelling) and microdosing method have been introduced into the process of drug development in recent decades. Adoption of these acts significantly accelerated intensive growth in the area of development of neonatal and pediatric drugs. Since 1997, a number of conducted clinical trials in children has increased by more than 5-fold; about 29,000 clinical trials in pediatrics and neonatology have been conducted by the end of 2022 [10, 11]. From February 1998 to May 2023, FDA approved 1049 amendments in pediatric drug labeling. It means addition of novel information about safety, effectiveness or dosage for novel and already applied drugs [12]. At the same time, no pediatric dosing recommendations are found in 2021 with the 9-year lag in pediatric instructions after approval of instructions for adults [13].

Microdosing in pediatrics — pilot pediatric trials

The guideline developed by the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use, ICH, M3, states that microdosing is a first-in-human trial, where drug exposure is less than that in phase I trial (less than the maximum tolerated dosage); it doesn't aim at producing a therapeutic effect and is not intended to assess tolerability [14]. The term 'an exploratory clinical trial' has been suggested. The European Medicines Agency, EMA, and FDA determine a microdose as 1/100 of the minimum predicted therapeutic dose obtained with extrapolation from the preclinical phase of animal trials or as a dosage not exceeding 100 mcg of the studied drug (or 30 nmol for biological ones) depending on what dose is the least. No therapeutic, toxic or radiotoxic doses (radioisotope labeling) are expected during exposure of such low doses. Though microdoses do not produce a serious effect and cause no effects in the body, various pharmacological effects produced by them can be detected using targeted approaches and sensitive analytical methods. Some authors refer to this type of studies, apart from exploratory clinical trials, as to phase 0 [15]. Basic barriers to using microdosing studies (exploratory studies or phase 0 approaches) among vulnerable population groups, and among children in particular, are of ethical nature and associated with safety. Three basic safety issues include drug exposure, procedural burden and radiation exposure. In microdosing studies, drug exposure is considered subtherapeutic and is identified as a minimal risk only. It represents a significant advantage over studies with therapeutic doses in vulnerable groups of population. In the pediatric population, the procedural burden is mainly associated with a number of blood samples. The WHO Guideline recommends to limit the volume of blood sampling, taking at least 3% of the total blood volume during 1 month and at least 1% of the total blood volume within 24 hours. The issue of procedural burden in a 3 kg newborn can be taken as an example. 1% of the total blood volume will be equal to 2.4 ml (1/100 of 240 ml). This blood volume can be taken from the patient within 24 hours. It can easily meet demands for sampling with liquid chromatography/mass spectrometry (LC/MS): 100 mcL per sample. Accelerator mass-spectrometry with a higher sensitivity also decreases the sampling requirements: 2 mcL per sample in total, depending on drug concentration.

Radiation exposure is low in PET, and extremely low in AMS, corresponding to the normal background exposure [15]. M. Turner et al. (2015) calculated radiation exposures using

microdosing methods in children. The radioactive dose was calculated using the worst half-life scenario of 40 days, with radioactive exposure ranging from 0.33 to 0.8 μSv.

It is much lower than the annual background exposure (2.5 μSv in the Netherlands), air travel within the European area (1–15 μSv), computed tomography (CT) of the head (1200 μSv) or chest X-ray (12 μSv). Thus, radiation exposure, which can be obtained during studies with AMS, does not exceed the minimum risk [16].

The study of microdosing in children is reviewed in the document entitled 'Additional warranties for children in clinical trials' cited in the FDA rules [17]. The principle of scientific necessity and risk assessment is described in this document. The ethical principle of 'scientific necessity' arising from the FDA rules states that pediatric studies are a must only if data obtained during the study refer to an essential need of public healthcare in pediatrics and can't be obtained from adults. The ethical principle requires to decrease the risks for subjects by way of excluding unnecessary procedures. The basic goal of pediatric clinical studies regulated by the FDA is to establish the dosage, safety, effectiveness of the studied drugs to an extent sufficient for licensing of both children, and adults. Additional means of protection of children included into the study consist of two basic categories: 1) in the lack of any perspective of getting a direct benefit for the included child, the studied product or procedure should represent at least an insignificant increase as compared with a minimal risk (i. e., a lower risk) in accordance with 21 CFR 50.51 / 21 CFR, or 50.53), or 2) the studied product or procedure should represent a perspective of direct benefit enough to substantiate higher risks (i. e., 'a higher' risk path in accordance with 21 CFR 50.52). In the last case, direct benefit should be obtained by a study participant and arises from a certain study intervention or procedure. As during the microdosing studies the administered dose of the studied drug is not sufficient to provide a therapeutic effect, the studies do not present an opportunity to obtain a direct benefit for a child. Thus, the microdosing studies should be assessed following the low risk. According to regulatory acts of the U.S., there are two categories of studies with a lower risk such as a minimal risk or insignificant increase as compared with minimum risk [4]. The minimum risk is defined as a 'probability and value of harm or discomfort expected in a study, which do not exceed those commonly found in a daily life or while accomplishing regular physical or mental examinations or tests' [4]. (Insignificant increase as compared with minimal risk can be allowed if additional criteria are followed). Intervention or procedure approved for this category should 'provide generalized knowledge about a subject's disorder or condition, which is essential for comprehension or improvement of the subject's disorder or condition'. Assessment of whether the intervention or procedure is just an insignificant increase as compared with the minimum risk should be done using enough data (for instance, any study-related pain, discomfort or stress won't be serious). The 'disorder or condition' is determined by the Institute of Medicine (IOM) as a set of 'specific physical, mental, psychomotor or social features', which, as per our scientific data or clinical knowledge, threaten a child's health or 'increase the risk of health problems in the future' (IOM). So, a child can be healthy, but subject to the risk of a disorder or condition taken as a study object.

The ethics of administration of subtherapeutic doses to children during studies of novel drugs has been discussed by the Pediatric Ethics Subcommittee (PES) of the Pediatric Consultation Committee created on May 11, 2011. Some factors that influence the risk assessment, including the quality of available data obtained during animal studies or how well the drug was characterized in adults, a child's age as related to the age of the population where the drug was studied, and the necessity of data obtained in adult studies of dose-dependent and dose-independent toxicity have been reviewed [18]. It has been decided that studies of subtherapeutic dosing can be conducted within the pediatric population if the preliminary favorable data were obtained after animal studies and studies of dose-dependent and dose-independent toxicity. So, pediatric microdosing studies should be of a scientific and social significance to correspond to the approval criteria. Second, as a microdose is insignificant to produce a therapeutic effect, pediatric microdosing studies should not be viewed in accordance with 21 CFR 50,52 (when direct benefit can be obtained by a study object). However, a drug microdose corresponds to the criteria of insignificant exceeding of a minimum risk and can be studied in children with a disorder or condition (disease or its risk), indicated by a study object. The FDA approves the use of microdosing studies in pediatrics. However, the issue of whether the microdosing studies can be approved among healthy children is still unsolved [19]. Nowadays, several microdosing pediatric studies have been conducted in the U.S. and Europe. The doses varied from 3 to 30 ng/kg with a set being 20 mcL per sample. The levels of administered radioactivity were extremely low. A linearity between the microdosing range and therapeutic dose was shown in the studies with such drugs as Ursodiol, Midazolam and Acetaminophen. The obtained data testify in favor of subsequent studies of other drugs and involvement of other vulnerable groups of population into studies. Of special interest is studying ontogenesis in children, especially metabolism, transport and excretion of drugs while changing the functional activity of organs using the microdosing method.

Thus, in the study of Mooij MG et al. (2017), a significant decrease of the relative rate of paracetamol sulfation has been demonstrated; intense glucuronidation processes during the first 6 years of life after single peroral administration of Acetaminophen have been confirmed. Thus, the effect of age on perorally administered metabolism of Acetaminophen has been studied in a minimal risk among children [20].

First pediatric dose

It is rather complicated to determine the first pediatric dose while developing drugs, because both effectiveness, and safety should be taken into account. It is unreasonable to administer a non-effective dose to a child (except for microdosing studies). Allometric scaling (when applicable), pharmacokinetics simulation, including physiologically substantiated pharmacokinetics models and pharmacokinetics/pharmacodynamics simulation, are used in clinical studies to improve dosing recommendations [21]. Ideally, every drug used in pediatrics should have pharmacokinetic and pharmacodynamic profiles, that will be reflected in guidelines on dosing and information leaflets. Unfortunately, the majority of pediatric drugs are currently lacking an evidence pharmacokinetics/pharmacodynamics basis. This results in the lack of empirical data to select a dose in people under 18 and significant variability in the amount and quality of data containing dosing recommendations. Many dosing recommendations are based on adult and animal data extrapolation in combination with various scaling principles. In the view of the existing situation, the principles of allometric scaling are currently taken as the best of the affordable means to select the most exact dosing regimen among 2-year-old children. Thus, they have

to be mentioned in dosing guidelines. According to the study conducted by Chitty KM et al. (2018), while analyzing the Australian Medicine's Handbook Children's Dosing Companion and British National Formulary for Children, it has been found out that dosing was done for 2% and 3.4% of drugs respectively using methods of allometric scaling [22]. The approach based on the dosage depending on body weight (mg/kg) is prevailing in the recommendations (about 2/3 of all analyzed drugs). In some cases, use of this approach results in more than two-fold deviation from the doses calculated with allometric scaling. This can be especially important for drugs with a narrow therapeutic range, where an exact dose assessment is necessary. Digoxin is an example of drugs with a very narrow therapeutic range. When the dosage of digoxin is calculated using the method of allometric scaling, the variability between the minimum and maximum doses occurs to a far lesser extent than the one observed when dosage is calculated based on the body weight. Thus, the risk of drug-induced toxicity can be minimized when a more exact dosage of Digoxin is selected [22].

Ethical issues of involving children in research

Participation of children in scientific studies has always been a subject of heated discussions and, as a consequence, a constantly changing field. As soon as the importance of research ethics and informed consent has been established, the debates about ethical issues associated with participation of children in studies continue in the U.S., Europe, Canada, etc. Historically developed opinion that has been predominant for a long time was that children should not participate in studies of drugs mainly for ethical reasons. In recent decades, a view on the problem has changed. The prevailing current opinion is that children deserve to participate in clinical studies of high quality and ethical standards, and obtain access to the drugs approved respectively. There is an argument stating that drug studies in children are essential to obtain evidence of safety and effectiveness of drug-induced therapy and cooperate in development of drugs against widely spread and essential pediatric diseases. Thus, ethical concepts that allow and even encourage participation of children in studies have been currently formed. It is increasingly being discussed that participation in studies won't be more than a minimum risk for a child. Though there is less probability that children will participate in phase I studies (except for children with oncological diseases), they will definitely have an ethical right to participate in phase II and phase III studies.

Another ethical conflict in pediatrics states that a consenting person (a parent or guardian) is not a person who receives therapy. There are growing calls for obtaining consent not just of parents, but also of children, especially adolescents, for ethical approval. At the same time, it is still unclear how informed consent to participation in the study can be solved best due to contradictions related to what a consent is and at what age the consent can and must be obtained. In many jurisdictions, the minors can provide an informed consent to various medical interventions, including the ones associated with a significant risk. However, they often fail to provide consent to participation even in studies with a very low risk. The aspect is still an area of active debates and discussions [23].

The draft Informed Consent Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors and draft Ethical Considerations for Clinical Investigations of Medical Products Involving Children contain the following recommendations: while taking a decision whether children are capable to provide consent, it's necessary to take into account the age, maturity and mental condition (mental abilities and stage of development) of children who plan to participate in the study. It is frequently believed that children aged 7 years and more can provide consent. The child does not have to gain a complete understanding of a clinical study to provide the consent if the child is able to understand interventions and associated procedures (for instance, blood sampling for analysis).

In accordance with these guidelines, children's consent is not a necessary condition for a clinical trial if: 1) children's capabilities are so limited that consultations can't be provided, or 2) intervention or procedure associated with a clinical trial can result in an indirect benefit, which is essential for children's health and well-being, and is available in the context of a clinical trial only. Under these circumstances, requirements to parental consent are preserved.

Meanwhile, even if it is established that children can provide consent, it may be unnecessary in the following cases: 1) a clinical trial is associated with a minimum risk for the subjects 2) refusal won't produce a negative effect on the rights and well-being of the subjects; 3) it's almost impossible to conduct a clinical trial without a refusal; 4) when appropriate, the subjects will be given additional respective information after their participation [24, 25].

The issue of acceptability

The issue of acceptability concerns a child's family, doctors, medical organizations, research centers and researchers. Historically, it was believed that parents are not willing to register their children in clinical trials. Based on the results of the conducted trials, it was assumed that the situation was rather apparent than obvious. An English and Canadian trial, and a trial held in France revealed that pediatricians who have not undergone ethical training, were unwilling to include children into clinical trials [4]. It becomes more obvious that children are interested in participation in the trials due to altruistic reasons and for the benefit of other children. The trial comfort level in children can be significantly different in various institutions. Regional and national pediatric trial networks, which can be the sources of standards and resources to improve developments and conduct clinical trials in children, can be a possible solution in this case. The National Institutes of Health Pediatric Pharmacology Research Network uniting research subdivisions in the U.S. can serve as an example. The Medicines for Children Research Network in the United Kingdom created by the National Healthcare Service and combining the experience in the area of pediatric research in the Great Britain should be mentioned as well. The Network created in the Great Britain was united with the Pediatric Specialty Group to create a clinical practice society generating the national experience in pediatric trials. It makes possible to exchange experience and practice [23].

The Pediatric Cluster organized in August 2007 by EMA and FDA is an example of international cooperation. The cluster represents exchange of information about drug development for children in the form of daily teleconferences between the regulating authorities of various countries. The objective of teleconferences is to ensure that all pediatric trials are held in compliance with strict scientific and ethical standards and that all pediatric patients are not subject to unnecessary (duplicate) trials.

The Pharmaceuticals and Medical Devices Agency joined the conferences in November 2009, whereas the Ministry of Health of Canada did the same in September 2010. They acted as observers. Nowadays, they are active participants of these

monthly data exchange. The Australia's Therapeutic Goods Administration joined the teleconferences in January 2014 being an active participant till now.

Monthly discussions include such issues as ethics and safety of pediatric trials, discussion of protocols, plans of pediatric trials, selection of efficacy endpoints, status of the current pediatric trials, outcomes of pediatric trials, plans of long-term safety monitoring, etc. This cooperation provides for safe ethical and scientific basis for these trials in children.

Clinical trials in neonatology

Review of 1,081 registered trials in children has shown that 74% of these trials were held in children elder than 2 years old. At the same time, changes in drug distribution and reactions to the drugs commonly predominate in children under 2 [26]. To protect children from unexpected unfavorable consequences in the majority of pediatric programs, researchers and regulating authorities select sequential developments, starting from trials for elder children and ending with trials for younger children.

However, following more than decade-long experience, a protective effect of using the sequential development has not been proven yet. At the same time, evidence of harm due to a long-term use of off-label drugs within the most fragile population (younger children) is indisputable [27]. In newborns, having clinical trials is a complex issue due to several reasons. There are knowledge gaps in the area of clinical pharmacology of newborns.

A few patients in neonatal trials can make it difficult to interpret the results of pharmacokinetics, pharmacodynamics or dose-ranging studies. It is even more complicated because the first month of life sees the growth, rapidly changing physiology and maturation of drug-associated receptors, metabolizing enzymes and transporters. These factors enable significant inter- and intraindividual variability of pharmacokinetics and pharmacodynamics, often observed in newborns [28]. Trials in premature newborns is even a more complicated issue due to unique pathophysiology and reaction to therapy within the population. Though about 200,000 premature newborns are annually admitted to intensive care units, very few drugs for therapy of this group of patients have been studied and approved. Drug development trials in newborns can be costly, risky and have ethical or practical limitations. In 65% of cases, intensive care units use not licensed and off-label drugs. As a rule, only one out of 10 drugs most frequently used at intensive care units is intended for premature children.

It means that irregular assignments, insufficient dosing, overdosing and unique or more frequent or more severe adverse effects are common in this vulnerable group [26]. In accordance with the Guidance on Clinical Trials of Drugs in Pediatrics adopted by the International Conference on Harmonization of Technical Requirements on Registration of Pharmaceutical Products for Human Use, studying drugs in premature newborns requires proper protocol development with participation of experts in neonatology and pharmacologists [24]. In rare cases, effectiveness of trials in adults and even in elder children can be extrapolated to premature newborns. Premature newborns are not a homogeneous group of patients. Body mass and gestational age can vary significantly, producing an effect on pathophysiology and reaction to drug-induced therapy [29]. For instance, a newborn who was born at 24 weeks gestation and is not under 4 weeks of age has physiology, which — during the first days of life — is different from the one of a newborn who was born at 28-weeks [30].

Thus, important features that should be taken into account with these patients during clinical trials include as follows: gestational age at birth and age after birth (corrected age); immaturity of renal and hepatic clearance mechanisms; protein (especially bilirubin) binding and exclusion; penetration of drugs into the central nervous system (CNS) due to the brain-blood barrier immaturity; unique diseases of newborns (respiratory distress syndrome of a newborn, open arterial duct, primary pulmonary hypertension); unique susceptibility of premature newborns (for instance, necrotic enterocolitis, intraventricular hemorrhage, retinopathy of the newborns); rapidly changing maturation of all physiological and pharmacological processes resulting in various dosing regimen in long-term administration of drugs, and increased transdermal absorption of drugs and other chemical substances. The issues of trial design that should be taken into account include as follows: weight- and age-related stratification (gestational and postnatal ones); small volumes of blood (40 ml of blood in a newborn with 500 g of weight); a limited number of patients; and difficulties in outcome estimation [29].

Out of 1,043 changes in the labelling of drugs approved for use in pediatrics by the FDA from 1999 to 2022, only 79 were allowed to be used among newborns. It should be noted that changes in drug information can be introduced even if no trials on newborns were conducted. For instance, safety information based on non-clinical data (for instance, data obtained in animal trials) can be included. Thus, out of 79 drugs with information about their use among newborns, only 57 underwent trials involving the age group [31].

A special amendment stimulating to conduct respective trial in newborns was proposed to the FDA Safety and Innovation Act adopted in 2012. In 2015, Wang J et al. studied databases of the FDA and found 43 drugs studied in newborns from 1998 to 2014. Twenty of them were approved to be used in newborns [28]. For 10 drugs, the approval was based on effectiveness data in newborns supplemented by pharmacokinetic data for four drugs. Approval for newborns was based on complete extrapolation of data from elder patients for six drugs, whereas partial extrapolation served as a basis for four of them. The majority of drugs studied in newborns were intended to treat infectious diseases (44%). Proton pump inhibitors to treat gastroesophageal reflux disease were the second most common ones (28%). Four drugs (famotidine, remifentanil, rocuronium and fenoldopam) out of those approved for use in newborns were tested with the dosing range and endpoints of pharmacodynamics to select the dose for subsequent phase III trials of effectiveness. Only three drugs (meropenem, linezolid and lucinactant) had dosing recommendations for premature newborns. Linezolid and meropenem required various dosing intervals for premature and mature newborns due to differences in pharmacokinetics within these two groups, whereas lucinactant was approved in premature children only. The label for the three products clearly states that these drugs are contraindicated in premature newborns because of their toxicity (lopinavir/ritonavir), non-effectiveness (nitrogen oxide to prevent bronchopulmonary dysplasia) or a lack of trials to support dosing recommendations (sevoflurane) [28].

Failures in the pediatric clinical trials

J. Momper et al. (2015) show that 42% of pediatric trials conducted from 2007 to 2014 failed to establish neither safety nor effectiveness of the studied drugs [32]. Thus, 44 unique drugs presented for review to the FDA were not labeled as approved for pediatric use. The main reasons for failures during pediatric trials included insufficient effectiveness (38 drugs, 86%) and safety issues (7 drugs; 16%). Bioanalytical

deficiency (saquinavir trial) and a lack of the delivery system necessary for young patients (fluticasone/salmeterol trials) were classified as other failures. It has been established that properly selected dose was a failure in ten trials where effectiveness was not established. Effectiveness was not displayed in 8 drug development programs due to impossibility to take into account basic differences in diseases of adults and children. Actual examples include differences in immune tolerance in children and adults (adefovir trial), differences in ADP platelet aggregation test (clopidogrel), differences in the role of acid in GERD pathogenesis (esomeprazole, lansoprazole, omeprazole and pantoprazole), differences in manifestations in case of herpes simplex virus (famciclovir) and differences in hypertension etiology (eplerenone). It was established that the rate of failures in pediatric trials is doubled up, when complete effectiveness extrapolation from adults is impossible. Knowing the natural anamnesis of a pediatric disease is essentially important to develop pediatric trials and select the basic effectiveness endpoint [32]. Improper or incomplete comprehension of pathophysiology of many conditions hampers detection of clinically significant biomarkers of pharmacodynamics. An example can include the use of gastric pH as an activity marker of proton pump inhibitors in treatment of symptomatic gastroesophageal reflux disease in newborns. It is currently comprehended that though newborns may have some signs and symptoms of gastroesophageal reflux disease, including regurgitation, vomiting and dyspnea, they probably have no gastroesophageal reflux disease mediated by acidic gastric content. Meanwhile, acidic gastric content is the basic pathophysiological factor of gastroesophageal reflux disease in elder children and adults. Symptoms of a gastroesophageal reflux disease in newborns are mainly associated with motility and abnormal temporary relaxation of the lower esophageal sphincter. The lower esophageal sphincter becomes mature by 34 weeks and occurs postnatally in newborns born before 34 weeks. Complete maturation of the sphincter occurs within 13 months. Besides, pH suppression in newborns can be irrelevant as the gastric pH in newborns can exceed 4 [28]. As a result, differences in pathophysiology of symptomatic gastroesophageal reflux disease in newborns as compared with elder children and adults resulted in failure of four clinical trials in infants (esomeprazole, lansoprazole, pantoprazole and omeprazole) [32]. Thus, in newborns, infants and children under 18 months, therapeutic benefit of proton pump inhibitors is not clear and can be limited by subpopulations, for instance, in those diagnosed with erosive esophagitis. In these cases, effectiveness of proton pump inhibitors can be extrapolated from adults along with clinical trials to determine a proper dose and assess safety [28].

Other examples when differences in disease progression could contribute to the inability of pediatric trials to display effectiveness include trials of migraine in adolescents and trials of type 2 diabetes mellitus in adolescents and children. Adolescents have shorter migraine attacks as compared with adults. So, patients can feel spontaneous pain relief during assessment of a typical primary endpoint (i. e., 2 hours after treatment). It hampers demonstration of a statistically significant difference between a drug and placebo. Similar to that, in children and adolescents, 2 type diabetes progresses more rapidly than in adults. This can be associated with a more rapid development of beta cell dysfunction. The real importance of these differences is unclear. Nevertheless, long-term trials have shown that the rate of failure while providing metformin therapy to children with type 2 diabetes mellitus is higher as compared with published data in adults. Moreover, effectiveness in children with type 2 diabetes mellitus failed to be displayed in several trials (glimepiride, rosiglitazone and a combination of fixed doses of glyburide/metformin) [32]. In pediatric patients, high placebo response was a factor leading to a failure in trials of products for therapy of bipolar disorder in children (divalproex) and major depression in children (duloxetine).

The diseases can have a different course in adults and in children. Apart from that, non-correspondent placebo reaction is an additional factor, which can be associated with failures in pediatric trials. Weimer et al (2013) studied placebo effects in children and its causes and concluded that the placebo effect had a negative correlation with age. Thus, in pediatric patients the placebo effect is pronounced to a greater extent than in adults [33].

Drug development for the treatment of rare diseases

Development of drugs to treat rare diseases in children represents a separate and no less important problem. A significant number of people (about 30–40 million European and about 25 million North Americans) suffer from orphan or rare diseases [34]. A single definition of orphan diseases is lacking.

According to Federal Law No. 323-FZ ‘On fundamental healthcare principles in the Russian Federation’, in our country, orphan diseases include diseases with the incidence of at least 10 cases per 100 thousand of people [35]. In the European Union (EU) and Canada, the threshold prevalence includes 5 cases and below per 10 thousand of people [35]. In the U.S., a disease is considered rare when it occurs in less than 200 thousand people [4].

It is important to note that about 80% of orphan diseases are of genetic origin. All the rest is the result of bacterial or viral infections, autoimmune or degenerative disorders. The majority of rare diseases (75%) are manifested within the first 5 years of life [36]. Orphan diseases go through all demographic population groups and all areas of medicine. At the same time, they are often diagnosed during the neonatal period of a child’s development. The majority of rare diseases relate to oncology, oncohematology and neurology. Many rare diseases produce mortality in children. 30% of children do not reach the age of 5 due to the prognosis of fatal diseases and lack of treatment. So, urgent innovations and accelerated drug development are required. While developing drugs to treat rare diseases, three basic principles such as urgency, a limited number of patients and need in complex planning of trials at early stages of development are essential. To improve the dose selection on the accelerated way, clear understanding of accessible information and knowledge gaps is necessary. The type of required therapy (biocorrection or targeted therapy) is of decisive importance. The diseases that need biocorrection with protein and enzyme replacement therapy such as hemophilia or Gaucher disease can be characterized by proper levels of concentrations, physiological pathways and biomarkers.

Nevertheless, as the diseases are rare, complete information about pharmacokinetics and safety, and reliable data about endogenous protein ontogenesis in healthy people can be lacking. As far as targeted treatment methods go, pharmacokinetics and safety data are easy to obtain from trials on healthy volunteers. However, it is more complicated to determine the optimal targeted reach and subsequent extrapolation of data from healthy people to patients. Early dosing data can be obtained from phase I (first-in-man) trials. For instance, the effect of dose on the muscular and adipose mass in programs studying Duchene muscular dystrophy was assessed by way of

registration of women in post-menopause during the first-in-man study, as these women, just like patients with Duchene muscular dystrophy have a decreased muscular mass and increased body fat mass. Extrapolation of data from adults to children becomes an essential problem that has to be solved at early stages of clinical trials, especially when the course of the disease in children is different from that in adults, is the principal problem that has to be solved at early stages of a clinical trials.

Data of clinical pharmacology and methods of mathematic modelling can be used to determine the relations between adults and children [37, 38]. Pediatric trials commonly include less subjects as compared with adult trials, whereas a small number of patients with rare diseases just makes the situation more complicated. Innovative plans of trials (adaptive design, Bayesian approach, randomized output method) help adjusting the trial to small groups [4]. Thus, development of drugs to treat rare diseases needs an accelerated process, implementation of innovations, and a reasonable approach to a few patients available. It is stressed that the area needs to develop phase I trial with a large bulk of data, wide use of modelling methods and various sources of information.

Perspectives on pediatric drug development

It should be re-emphasized that it is now the most promising time for development of pediatric drugs. Two international networks of pediatric trials have been developed. Owing to coordinated efforts of the pharmaceutical industry, scientists and regulating authorities, tremendous progress has been made concerning comprehension of age-related changes in drug distribution, especially the drugs associated with oxidation and transportation in the liver [26].

The priority tasks for today include a continued search for non-standard approaches to pediatric drug development and support of an open and reliable dialogue between the interested parties (for instance, regulating authorities, drug developers, academicians, patients and suppliers of medical services) regarding the strategies of pediatric product development and ensuring safe and effective use of drugs in children. Development of pediatric drugs is taken by the world as a global task. Thus, policy and practice of regulating in this area should be agreed upon to the greatest extent. Various activities that promote advanced discussions on pediatric product and trial development, including monthly teleconferences, joint working groups, seminars and expert meetings, are conducted for this purpose [4]. With the introduction of the abovementioned legislative changes, a number of pediatric clinical trials and applications to prolong the patent has increased. As of May 2023, over 1,040 names of drugs were reviewed with addition of data for pediatric use [12]. Moreover, dosing and toxicity data were included for many drugs. Continuous work to support and stimulate pediatric trials resulted in significant success in approval of novel and older off-label drugs in pediatrics.

CONCLUSIONS AND RECOMMENDATIONS

For at least 50 years, it has been stated in patient information leaflets that safety and effectiveness in children were not assessed. It was a legal disclaimer when drugs were used in children. Since the middle of 1990s, regulating authorities of a number of countries have adopted laws, regulatory acts, and compensatory measures for developing companies to increase a number of clinical trials in pediatrics and neonatology. Since the middle of 2000s, a significant growth of these trials has been observed. At the same time, many issues such as ethics, continuity and selection of a dose for trials are still disputable. Newborns belong to a special group, whereas premature newborns are even more vulnerable. Though many global regulating authorities approve the trials in pediatrics, the issue has not been solved yet.

On the one hand, inclusion of children into clinical trials can ensure rapid access to safe and effective drugs for children. On the other hand, participants of pediatric trials can test ineffective or not safe products that will never be approved for or reach the market. Searching for a reasonable balance between these two ethical principles remains relevant even today.

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HOSPITAL-BASED ABC ANALYSIS OF PHARMACOTHERAPY IN KIDNEY AND LIVER TRANSPLANTATION

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Liver and kidney transplantation is the most effective and frequently the only radical method of treatment of patients with end-stage chronic kidney/liver diseases. Expenditure on transplantation is rather high. A number of patients with a reduced function of kidneys or liver is increasing rapidly. Thus, the problem is pressing and interdisciplinary. It has serious social and economic consequences for the Russian Federation. In this respect, analysis of the structure of use of medicinal preparations (MPs) enables to rationalize their application in clinical practice. This allows to carry out targeted measures to improve costly drug-induced therapy. Having analyzed prescriptions, it has been found out that MPs related to 52 pharmacotherapeutic groups were used in pharmacotherapy during kidney and liver transplantation within the analyzed period. ABC analysis revealed preparations included into group A, a group of immunosuppressants with the largest costs.

Key words: liver transplantation, kidney transplantation, chronic kidney disease, liver failure, ABC analysis, cost structure

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АВС-АНАЛИЗ ФАРМАКОТЕРАПИИ ТРАНСПЛАНТАЦИИ ПОЧЕК И ПЕЧЕНИ В УСЛОВИЯХ СТАЦИОНАРА

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Трансплантация печени и почек является наиболее эффективным и часто единственным радикальным методом лечения больных с терминальной стадией хронических болезней почек/печени. Затраты на трансплантацию достаточно высоки. В популяции достаточно быстро растет число пациентов со сниженной функцией почек или печени. Именно поэтому данная проблема является актуальной и междисциплинарной, имеющей серьезные социально-экономические последствия для РФ. В связи с этим анализ структуры использования лекарственных препаратов помогает рационализировать их применение в клинической практике, что позволяет проводить целенаправленные мероприятия для оптимизации дорогостоящего медикаментозного лечения. Проанализировав назначения пациентов, получили, что в фармакотерапии трансплантации почек и печени за анализируемый период были использованы ЛП 52 фармакотерапевтических групп. АВС-анализ определил препараты, которые входят в группу А — группу иммунодепрессантов, на которую приходятся наибольшие затраты.

Ключевые слова: трансплантация печени, трансплантация почек, хроническая болезнь почек, печеночная недостаточность, АВС-анализ, структура затрат

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Kidney and liver diseases hold a prominent place among disorders associated with the loss of labor capacity and need in high-cost therapy due to significant prevalence in the population, rapid decline of life quality, and high mortality of patients. They also result in the need of using costly methods of replacement therapy in end-stage disease such as dialysis and kidney transplantation [1].

Chronic kidney disease (CKD) is a gradual damage or loss of kidney function over 3 months under the influence of various etiological factors. Its anatomical basis is replacement of normal anatomical structures with fibrosis, which results in its dysfunction [2].

Liver failure occurs when the liver can no longer function. There is acute liver failure (quick loss of liver function that occurs during several days or weeks) and chronic liver failure (a slow decline in liver function during months or years).

Prevalence of chronic kidney and liver disease can be compared with such socially significant diseases as hypertension, diabetes, obesity and metabolic syndrome. Signs of kidney damage and/or decrease in glomerular filtration rate are found among at least every tenth representative of the general population [1].

Kidney and liver transplantation is currently the most effective and frequently the only radical, though costly, method of treatment of patients with end-stage chronic kidney/liver diseases.

Rapid growth of a number of patients with an impaired function of kidneys and liver is not a highly specialized, but general medical interdisciplinary issue with serious social and economic consequences for the RF.

Satisfied population needs in novel medicinal preparations with high effectiveness and novel medical devices relate to one of the most essential healthcare issues of the modern world [3].

Analysis of the structure of using medicinal preparations (MPs) allows to obtain data on their use in clinical practice, compare

countries, regions and various healthcare systems, and examine a change in the use of MPs over time. Examination of consumption of MPs allows to establish their non-rational use, and conduct targeted activities to optimize costly drug therapy [4].

Assessing the rational use of expenses on pharmacological support is one of the most actual tasks in modern healthcare.

The study objective was to perform ABC analysis of MPs used in hospital-based transplantation of kidneys and liver.

The objective of the research was to perform a pharmacoepidemiology analysis of MPs used during hospital-based transplantation of kidneys and liver.

MATERIALS AND METHODS

The study was carried out at a 200 bed multi-specialty hospital of Nizhny Novgorod, where both therapeutic and high-tech surgical aid was provided.

Medical cards of patients (n=34) who underwent pharmacotherapy during kidney and liver transplantation in 2018 and quarters I–III of 2019 were the study object.

ABC analysis of MPs used in therapy of kidney and liver failure was used throughout the study. All medicinal preparations were divided into three classes based on costs and taking into account their international non-proprietary name (INN): class A (10–20% of MPs with 80% of monetary funds spent), class B (10–20% of MPs with 15% of monetary funds spent), and class C (60–80% of MPs with 5% of monetary funds spent) [5]. ABC-analysis includes as follows:

1. Forming a list of MPs indicating trade names, prices per a counting unit used at a healthcare institution within a certain interval.
2. Calculating the percentage (%) of total expenditure: Total expenditure = (cost of MPs/ total expenditure on all MPs) × 100
3. Distribution of MPs in descending order of costs.
4. Calculating the cumulative percentage by summing up the percentage of expenses on every MP in descending order of their percentage in the sum of expenses.
5. Allocation of classes A, B and C.
6. Final analysis of every MP to determine whether it is reasonable to use the MP in case of certain nosological forms of diseases found at a healthcare institution in accordance with the profile of the rendered medical aid and acting clinical protocols [5].

The obtained data were utilized to form a database analyzed using MSO Excel and ABC-analysis. Expenses on the groups of MPs used in therapy during kidney or liver transplantation were estimated with the help of ABC analysis.

STUDY RESULTS

MPs from 52 pharmacotherapeutic groups were used in pharmacotherapy during the analyzed period. There were 98 positions of MPs as per INN.

The groups with MPs being used 3 or more times have been identified among pharmacotherapeutic groups. Other pharmacotherapeutic groups with MPs being used once or twice have been included into a separate group (table 1).

Table 1. Pharmacotherapeutic groups of MPs used in chronic kidney and liver failure

Pharmacotherapeutic group	Number of drugs, n (%)
Antimicrobial drugs	9 (9.19)
Beta-blockers	5 (5.10)
Proton pump inhibitors	4 (4.08)
Immunosuppressants	4 (4.08)
Regulators of water-electrolyte balance and acid-base balance in combinations	4 (4.08)
Macro- and microelements	4 (4.08)
Anticoagulants	3 (3.06)
Calcium channel blockers	3 (3.06)
Hematopoietic regulators	3 (3.06)
Diuretics	3 (3.06)
Hepatoprotective agents	3 (3.06)
Antiplatelet agents, adenosinergic agents, angioprotectors and correctors of microcirculation	3 (3.06)
Other preparations (1–2 administrations)	50 (51.03)
Total	98 (100.00)

In therapy of liver and kidney transplantation, the largest expenditure (group A) was for such a pharmacotherapeutic group as immunosuppressant medications (with 85.8% of share of expenses) (mycophenolic acid, immunoglobulin antimocytic and basiliximab) (table 2).

Priority MPs include mycophenolic acid with the largest expenditure (with 45.35% share of expenses) and immunoglobulin antimocytic (with 23.35% share of expenses).

Group B includes the MPs related to pharmacotherapeutic groups such as anticoagulants (with 3.84% share of expenses), regulators of water-electrolyte balance and acid-base balance including antidotes (with 5.51% share of expenses). These MPs were used both among patients who underwent therapy during liver and kidney transplantation, and among patients who were on supportive therapy.

Group C included the rest of MPs. Based on pharmacotherapeutic groups, it is possible to differentiate between quinolones/fluroquinolones (with 0.45% share of expenses) and hematopoietic regulators (with 0.35% share of expenses).

CONCLUSIONS

ABC-analysis is a relatively simple pharmacoeconomic tool, which allows a professional from a medical institution to assess whether the medicinal agents were used by hospitals in a reasonable way, and also to determine the most problematic issues of unreasonable use of medicinal agents.

Based on the results of the study it has been found out that MPs belonging to 52 pharmacotherapeutic groups were used in pharmacotherapy during the analyzed period. Total number of used MPs (as per INN) was 98. The conducted ABC analysis has shown that group A includes mycophenolic acid, immunoglobulin antimocytic and basiliximab (with 85.80% share of expenses), a group of immunosuppressive agents with the largest expenditure during kidney and liver transplantation.

Table 2. Expenditure on medicinal preparations of class A

INN	Course fee, RUB.	Frequency of administration	Total expenditure, RUB.	Share of expenses on MPs,%
Mycophenolic acid	296661.61	24	7119 878.82	45.4
Immunoglobulin antimocytic	282003.57	13	3666 046.42	23.4
Basiliximab	107392.81	25	2684 820.15	17.1

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