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И РОССИЙСКОГО НАЦИОНАЛЬНОГО ИССЛЕДОВАТЕЛЬСКОГО МЕДИЦИНСКОГО
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Guryleva ME[1], Nezhmetdinova FT[2] ✉

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New forms of medical aid have been widely used in the presence of global digital transformation of medicine. This concerns not only medical equipment and ensuring access to health services, but also the entire healthcare system and doctor-patient relationship. It's impossible to imagine modern medicine without digital decisions. Digitalization of the available information and making it available for all participants of the doctor-patient system form the basis of subsequent development of clinical practice, breakthrough in scientific research, improved patient-centered healthcare, and comfort of system operation for people. This requires a general culture of values and ethical standards that should correspond to digital decisions. The article deals with the reasons for actualization of remote forms of doctor-patient communication during the COVID-19 pandemic illustrated by telemedicine. Principle forms of telemedicine under modern conditions caused not only by the pandemic but also by digital transformation of medicine have been reviewed. Special attention is given to possibilities of telemedicine from the point of view of benefit, as well as to legal and ethical aspects from the point of view of risks.

Keywords: telemedicine, doctor-patient relationship, digital transformation of medicine, advantages, risks, ethics, law

Author contribution: Guryleva ME — selection of literature and sources; Nezhmetdinova FT — analysis of literature, defining subject-based patterns, interdisciplinary estimation of ethical risks.

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ТЕЛЕМЕДИЦИНА: ПРЕИМУЩЕСТВА И РИСКИ

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В условиях цифровой трансформации медицины в мире получили распространения новые формы оказания медицинской помощи. Это не только коснулось медицинского оборудования и организации доступности медицинских услуг, но и затронуло всю систему здравоохранения, взаимоотношений врача и пациента. Современную медицину уже невозможно представить без цифровых решений. Оцифровка имеющейся информации и обеспечение доступа к ней всем участникам системы «врач — пациент» — основа дальнейшего развития клинической практики, прорывов в области научных изысканий, повышения уровня пациентоориентированности здравоохранения, комфортности работы системы для людей. Это требует выработку общей культуры ценностей и этических норм, которые должны соответствовать цифровым решениям. В статье рассматриваются причины актуализации дистанционных форм общения врача и пациента в условиях пандемии COVID-19 на примере телемедицины. Рассмотрены основные формы телемедицины в современных условиях, вызванных не только пандемией, но и цифровой трансформацией медицины. Особое внимание уделяется возможностям телемедицины с точки зрения пользы, правовым и этическим аспектам с точки зрения риска.

Ключевые слова: телемедицина, взаимоотношения «врач и пациент», цифровая трансформация медицины, преимущества, риски, этика, право

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Telecommunication technologies appeared not today and not even yesterday, but owning to the restrictions of COVID-19, the so-called Black Death of the 21-st century, humanity came across a need to fundamentally change the interrelation process by limiting personal contacts to the maximum extent. Thus, remote methods of communication were developed. COVID-19 made humans look at communication both within and between the countries from a different perspective, produced a significant effect on organization and development rate of all spheres of a human activity, urged to seek for new possibilities of building interpersonal relationships. Under such conditions, medicine has been at the forefront as people still suffer from various diseases and require medical aid on a constant basis, whereas epidemiological limitations need new forms of safe interaction. Telemedicine has turned into a form of human interaction.

RELEVANCE

In his Address to the Federal Assembly, the President of Russia V. V. Putin has stated as follows: 'Healthcare information support should make a contribution to the increased accessibility of medical aid; it's necessary to establish electronic cooperation between medical institutions, pharmacies, doctors and patients within three years' [1]. And it makes so. Telehealth consultations constitute a relevant and operating method.

They can be conducted in real time or be delayed [2]. Online consultations require good technical means and provide excellent results. Thus, they allow communication of different medical specialists parted by distance, examine a patient here and now, interrogate a patient, hold a discussion and arrive at a collective decision, which is extremely important in case of a medical emergency, for patients without typical symptoms and with severe complications. Delayed consultations are effective, successful, and can be conducted by highly trained specialists from the leading clinics. Delayed (or asynchronous) telecommunications are commonly used to interpret X-ray films and other digital images, results of functional tests (for instance, ECG, spirography), and to assess their dynamics. The President's appeal was followed by development of Healthcare National Project. It is assumed that its implementation (including implementation of Telehealth Consultations subsystem) will enable to achieve the following goals of healthcare in the country: decline in mortality in the working-age population (up to key values of 350 cases per 100,000 of population), cardiovascular disease mortality (up to 450 cases per 100,000 of population), neoplasm related mortality including malignant ones (up to 185 cases per 100,000 of population), infant mortality (up to 4.5 cases per 1,000 of newly born babies); mitigation of staff shortage in medical organizations providing primary health care; optimal availability of medical aid for population (including residents of remote populated areas); and optimizing healthcare organizations [3, 4].

HISTORICAL BACKGROUND

The idea of telecommunications is not new. The first remote visual examination of children was carried out in 1924. Later telehealth consultations were used to control health of sailors and astronauts. Doctors have been using the Internet for remote monitoring of patients' condition, storage and transfer of data since the 1990s [5]. Remote monitoring is especially good to control health of cardiac patients, patients with diabetes mellitus, and subjects participating in clinical trials [6]. The term 'teleconference' has become part of contemporary practice. But it must be remembered that using a telehealth consultation is the right of both a doctor, and a patient; and this right should not prevent patients from obtaining medical aid in person, but needs just add to it, as solicitation of medical services is inadmissible. It's not an intention to avoid personal conversation with a patient, but a forced necessity. Provision of medical care through telehealth consultations is not a separate type of a medical activity. It is used as a technology constituent when performing works not included into a medical activity [7, 8]. In our country, telehealth services are covered with compulsory health insurance based on targeted tariff agreements generated by regional Territorial Funds of Compulsory Medical Insurance, regional public authorities and insurance companies, additional medical insurance and personal finances.

According to the World Health Organization, telemedicine is provision of aid to healthcare specialists who use information and communication technologies to exchange the required information for diagnostics, treatment and prevention of diseases and traumas, conduct trials and estimate the results, and ensure continuous education of medical specialists in order to improve population health and develop professional communities [2].

Among information and communication technologies (IT-technologies) used in medicine, telehealth technology is most widely utilized to support decisions, manage (material and intellectual) resources, optimize logistics and interaction between different medical institutions and levels of medical aid. Telemedicine standardizes values of accessibility and quality of obtained medical aid and is absolutely irreplaceable when the geographic distance between a patient and a healthcare professional is a critical factor. Telemedicine is implemented in two directions: 1) when doctors interact with patients and their relatives; 2) among medical workers. The basic trends in telemedicine for the 'doctor-patient' system are represented by remote online, and delayed medical consultations at all stages of medical work (when rendering primary, specialized, high-tech, urgent, palliative medical care), home telemedicine (especially for remote and hard-to-reach areas), and control of health in limited groups (military personnel, sportsmen, participants of clinical trials) [6, 9]. The doctor-doctor system successfully uses telecommunication-based education (almost the entire system of continuous medical education (CME) is based on remote methods — edu.rosminzdrav.ru -, streaming surgeries live), holds urgent consultations of severely ill and emergency patients, and conferences on the basis of the Federal Telehealth System of the Ministry of Health of the Russian Federation (http://tmk.rosminzdrav.ru) [9, 10] generating an electronic medical opinion. Medicinal agents (including narcotic drugs or psychotropic substances) can be prescribed remotely. E-prescriptions are sent directly to allocated pharmacies where patients can obtain medicinal agents prescribed by doctors [11]. If a patient needs prescription to treat a condition that wasn't confirmed during a personal visit, it is necessary to visit a real medical institution as medicinal agents can't be virtually prescribed in this case.

BENEFIT

Telehealth communication has a number of benefits over a traditional doctor's appointment. It can be used when a patient is located in hard-to-reach places, allowing patients from different territories to obtain qualitative aid, and is economically reasonable. With a growth of healthcare expenses in the majority countries (in the U.S., they reached 20% of GDP by 2020), telehealth allows to optimize costs saving doctor-patient time, increasing effectiveness of medical institutions, and reducing a number of doctors' mistakes [12]. Meanwhile, telehealth development is not cheap and inhibited by financial, technical and cultural factors. The first ones include equipment and costly software purchase costs. Computer competence and ability to use equipment both by doctors, and patients is a complex issue. The same is true for organization of training for all parties of the therapeutic and diagnostic process, technical support, and availability of the corresponding infrastructure. Logistical restrictions are associated with accreditation of this type of medical aid provision [13].

A medical institution can be accredited for telehealth service provision only in the presence of a premise equipped in accordance with licensing requirements and when patients go through compulsory identification through the Unified Identification and Authentication System (UIAS). It means that telehealth services can be provided only to the citizens with a validated account on the State Services portal (https://www.gosuslugi.ru/), but not to the entire population including the elderly (who don't commonly have proper computer skills and are not registered in the social network), and only at those medical institutions that correspond to the submitted requirements. Moreover, it is obligatory for healthcare professionals to use the Integrated National Information Healthcare System (INIHS): only those physicians included into the Federal Registry of Doctors can provide medical aid [14]. According to the law, a

doctor can provide telehealth services only from the workplace equipped in accordance with licensing requirements, and using the equipment of a medical organization only, etc. Software must comply with all requirements of information safety of the Federal Service for Technical and Export Control, Federal Security Service of the Russian Federation, and Ministry of Health of the Russian Federation [15]. In this case, an issue about **accessibility of medical care** has been raised. It poses a serious ethical problem.

ETHICAL RISKS

Doctor-patient telecommunications require the same conditions as personal communications and exercising all the rights of patients stated in the Declaration of Policy Concerning Patients' Rights in Europe [16], Declaration of Patient's Rights in Russia [17], and Federal Law No. 323-FZ 'On fundamental healthcare principles in the Russian Federation' [18]. First and foremost, it is about **voluntary informed consent** to medical intervention or refusal from such consent and preservation of **confidentiality**. A healthcare worker can't take a medical history, conduct an examination, perform diagnostic and therapeutic activities without a patient's preliminary written consent. When performed online, all the stages of communication with a patient are specific with possible violations of the patient's rights being significantly expanded. A vast amount of confidential information is transferred via the Internet. It can include video files, audio files, texts in the form of medical reports, medical notes, case records, etc. It is exchanged between medical institutions or between medical institutions and medical aid consumers (patients).

Taking into consideration the possibilities of telecommunications, the procedure of healthcare information support is improved. Thus, the Integrated National Information Healthcare System (INIHS) was created containing personal record-keeping data and data of federal healthcare registers, data about medical organizations that provide aid to patients, their medical documentation, data about provided high-tech medical care, and supply of citizens with discount prescription drugs, etc. [14]. The electronic trace data can be posted on the State Services portal (medical certificates, COVID-9 immunization status data, etc.) [19]. This is definitely associated with ethical risks.

In Russia, much has been done during the last decade for legal support of IT-technologies in medicine. Amendments introduced to the Law 'On fundamental healthcare principles in the Russian Federation' [18] regulate the possibility and procedure of remote informed consent of a patient to medical intervention. The Law 'On personal data' describes the principles of personal data processing in state and municipal information systems, rights of personal data subjects existing during such processing, obligations of an operator who acts as a doctor-patient mediator when IT-technologies are used in medical practice [20]. Order of the Ministry of Health of the Russian Federation as of November 30, 2017 No. 965н 'On approval of the procedure of provision and rendering medical aid using telehealth technologies' and Letter of the Ministry of Health of the Russian Federation as of April 09, 2018 No. 18–2/0579 'On the procedure of provision and rendering medical aid using telehealth technologies' that regulate the telehealth method of providing medical health to patients [9, 15]. Separate telehealth standards are included into Government Resolution of the Russian Federation as of May 05, 2018 No. 555 'On the Uniform State Health Information System' [14]. However, there is still much room for improvement.

LIMITATIONS

In accordance with the law, remote patient observation can be provided only following an in-person consultation (examination, appointment); remote correction of previously assigned treatment is justified only if the diagnosis was established and treatment was assigned during a face-to-face consultation with a doctor [18] (Federal Law No. 323-FZ 'On fundamental healthcare principles in the Russian Federation' (2011), art. 36.2 'Peculiarities of medical aid provided using telemedicine technologies'), i. e. a physician has no right to *make* remote diagnosis. Moreover, the Ministry of Health of the Russian Federation sets neither stages of medical aid provision with the use of telehealth technologies, nor structural subdivisions providing this aid that would define minimal equipment of 'a doctor's virtual room'. All this inhibits development of the trend of medical aid provision.

Introduction of new information technologies into medical practice without the corresponding legal support is associated with the risk of litigation involvement [21]. It is a vicious circle: there is a need but no technology is developed; there is liability but not a possibility to prevent it. The Federal Law No. 258-FZ 'On experimental legal regimens in the sphere of digital innovation' [22] was put into force in January 2021. It permits testing of those technologies that can't be regulated yet due to the law constraints (artificial intelligence, blockchain, big data, neurotechnologies, quantum technologies, virtual reality) but would partially settle the defined problem for a limited number of users on a certain territory and during a limited period of time [22]. It is suggested that a special procedure of determining the tariffs of compulsory medical insurance for telehealth consultations and other healthcare digital solutions be implemented. Then use of telehealth consultations and medical decision support systems could be reimbursed with the resources of the Compulsory Medical Insurance Fund.

Cultural limitations of using telehealth technologies are associated with national and age-related preferences of treatment and diagnostic process participants. Thus, the elderly patients prefer face-to-face communication with a doctor, and not all the doctors are ready to provide the aid due to available traditions. It seems that generation Z will be the principal user of this technology.

CONCLUSIONS

Use of telemedicine can violate information safety (violation of patients' personal data safety and breach of confidentiality/medical privacy). Federal Law as of July 27, 2006 No. 152 'On personal data' states that data concerning seeking medical advice, health and diagnosis, other data obtained during a patient's examination and treatment constitute doctor-patient confidentiality [18, 20]. Criminal (art. 137 of the Criminal Code), administrative (art. 13.11 of the Administrative Code) and/or civil liabilities are established for exposing data about the confidentiality [23, 24].

As telehealth consultations are provided through the Internet, data leakage is not excluded with the liability resting with the consulting medical institution. Requirements to the servers with patient-related data and the procedure of access thereto have not been set. It is implicit that when processing and storing the data it's necessary to use data storage and encryption systems and implement other measures associated with personal data storage. However, the data are not regulated in the legislation yet [25]. Moreover, it is

difficult to imagine that physicians can independently deal with information technologies, they need such intermediates as operators. Requirements to the operators who are not medical activity participants but who ensure that patients have access to telehealth services (providing information about medical organizations, online booking an appointment with a doctor, storage of materials, obtaining, acquisition and presentation of data, etc.) are regulated only partially [26]. Operators are not medical workers, they have to protect data from unauthorized access, elimination, modification, blocking, copying, presentation, and distribution, but they take no responsibility for violation of confidentiality [27]. It is obvious that the problems are intensified due to COVID-19 pandemic [28].

Patient identification is an ethical problem too. It is difficult to identify who provides consent at a distance. According to the law, informed consent can be provided either in hard or soft format. Soft format means a document signed with an enhanced encrypted and certified digital signature or a simple electronic signature using the USIA or a document signed with an enhanced encrypted and certified digital signature of a medical worker [18]. Getting the signature is rather difficult. It significantly influences a wish (and possibilities) of patients and medical workers to use the services and ultimately inhibits telehealth development. Subsequent use of a patient's account doesn't mean that this is done by the patient and not by somebody else challenging the very essence of the patient's voluntary informed consent (geriatric population, patients with narcological and mental disorders, etc.) The issue about anonymous highly-demanded consultations is not settled at all. As a 'telehealth' patient has to enter the portal of public services via his/her record entry only, no anonymity can ever be involved.

Thus, being a technology of communications that facilitates human interactions, telemedicine occupies its own niche and is steadily expanding the sphere of activity. Multiple ethical and legal issues still remain and require to be explored for subsequent development of this direction.

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REVIEW OF 'ETHICAL EXAMINATION IN BIOMEDICAL RESEARCH: PRACTICAL CONSIDERATIONS' FOR ETHICS COMMITTEES (THIRD EDITION, REVISED AND ENLARGED) UNDER THE GENERAL EDITORSHIP OF KHOKHLOV AL

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The article reviews the edition known as 'Ethical Examination in Biomedical Research: Practical Considerations' (third edition, revised and enlarged) under the general editorship of Professor Khokhlov AL, a corresponding member of the Russian Academy of Sciences. Due to a constantly growing number of clinical trials of medicinal products and improved level and quality of medical technologies, the role of an ethical examination aimed at compliance with ethical rights of trial participants and consumers, and safety aspects is increased. The article sums up what was described in the published edition.

Keywords: clinical trials, ethical examination, personal data, ethics committees, biobanking, international standards

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ОБЗОР РУКОВОДСТВА ДЛЯ КОМИТЕТОВ ПО ЭТИКЕ «ЭТИЧЕСКАЯ ЭКСПЕРТИЗА БИОМЕДИЦИНСКИХ ИССЛЕДОВАНИЙ: ПРАКТИЧЕСКИЕ РЕКОМЕНДАЦИИ» (ТРЕТЬЕ ИЗДАНИЕ, ИСПРАВЛЕННОЕ И ДОПОЛНЕННОЕ) ПОД ОБЩЕЙ РЕДАКЦИЕЙ А.Л. ХОХЛОВА

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Статья посвящена обзору вышедшего в свет издания «Этическая экспертиза биомедицинских исследований: практические рекомендации» (3-е издание (испр. и допол.), под общей редакцией члена-корреспондента РАН, профессора Хохлова А. Л. В связи с постоянно растущим количеством клинических исследований медицинских продуктов, а также повышением уровня и качества медицинских технологий возрастает роль этической экспертизы, направленной на соблюдение этических прав участников исследований и потребителей, а также аспектов, касающихся их безопасности. Статья описывает краткое содержание опубликованного издания.

Ключевые слова: клинические исследования, этическая экспертиза, персональные данные, этические комитеты, биобанкинг, международные стандарты

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Ethical aspects of human and animal trials are a source of concern for the society. Pharmaceutical companies that conduct the trials are subject to criticism because of poor transparency. Moreover, it is asserted that the trials of approved and commercialized medicinal agents are conducted mainly for marketing purposes or abroad to cut expenses or bend strict rules [1, 2, 3].

Ethical aspects of clinical trials are set in the Declaration of Helsinki. It's an ethical standard developed in 1964 that regulates human trials. Additional standards, regulations and ethical codes that guarantee the primary importance of safety and human well-being during the trial have been developed and implemented since then [4].

New challenges of modern healthcare promote constant improvement of approaches to diagnostics and treatment of various diseases [5, 6, 7]. Such issues as duration and quality of life, possibilities of medical and social support, rehabilitation and habilitation of physically disabled society members are top priority for scientists, public men and politicians globally. To estimate safety and effectiveness of new methods, it's obligatory to conduct clinical trials, the results of which allow to implement new technologies in clinical practice [8].

It means that a number of projects with participation of laboratory animals in experimental methods, healthy volunteers, patients with various diseases and a total number of trials will not be reduced. Novel medicinal agents, medical devices, diagnostic procedures appear, genetic trials, trials of regenerative medicine, biomedical cellular products, information, reproduction and other technologies are carried out actively [9].

Clinical trials of brand-new medical technologies that haven't been used before are associated with some ethical issues. Scientific value of the results obtained during clinical trials must be in compliance with ethical standards [10, 11].

Modern interest to ethical and legal issues of biomedical human research is due to a number of reasons. Today their scope, range of tasks and practice undergo violent changes. Biomedical trials have lately become extremely important, necessary and essential from the economic point of view. It should be taken into consideration that many laws, orders, instructions and provisions acting in the Russian Federation and members of the EAEU require renewal and bringing to conformity with modern international requirements.

THE MAIN PART

As the topic is highly relevant, the guideline known as 'Ethical Expertise of Biomedical Trials' has been prepared. A large team

of writers including clinical pharmacologists, pharmacologists, specialists in bioethics, sociology and philosophy of medicine, clinicians, health professionals, those involved in medical education, regulatory authorities, and lawyers participated in creation of the guideline under the aegis of the Russian Academy of Sciences.

The guideline reviews pressing topics related to compliance with ethical principles. First and foremost, it deals with the history of ethics in medicine as a separate branch that comes through constant changes, and presents doctors' mistakes that were subsequently analyzed with their minimization methods being addressed.

Recommendations on establishment and activity of ethics committees, including international standards, basic ethical principles and fundamental documents, standard operating procedures are presented. The chronology of creating the legal base as the basis for ethical review has been described. Real examples of ethical reviews in the Eurasian Economic Union have been presented. Practical recommendations on establishment of the charter of the ethics committee are provided in detail; purposes, tasks, objectives and authorities of ethics committees are specified.

Standard operating procedures of ethics committee are described in a separate chapter. A standard operating procedure is a document that deals with the procedures used by the committee and where the committee's policy is reflected. The written guideline states as follows about the Ethics Committee's procedures: 'describe the operating procedures step by step and with enough details to make an outsider understand how the ethics committee functions and how it performs its principal functions'. Every ethics committee must create and subsequently follow an own set of instructions a point of application and sphere of influence of which reflect the activity of this committee and correspond to the national and international standards of ethics expertise of research and legislative regulations. The data presented in this chapter need to be used by ethics committees of all levels to develop and correctly select standard operational procedures. The procedure and inspection of ethics committees with controlling functions are also described to assess the quality of the conducted expertise.

The guidelines contain detailed requirements to preparation of documents to assess whether it is possible to conduct clinical trials. An informed consent form is given special attention. The document with key functions is of primary importance. On the one hand, it is intended for a participant of the clinical trial. It is written in accessible language and provides clear understanding of the situation. On the other hand, the document allows to conclude that the subject voluntarily consented to participation and that his/her rights are not restricted. The procedure of obtaining informed consent from vulnerable groups (disabled people, minors, incurable persons) is separately described. A separate chapter is devoted to obtaining an informed consent.

The principles of protecting personal data of trial subjects, insurance of trial participants, differentiation and interrelation between clinical trials and real clinical practice are also examined. Specific considerations of an ethical review including vulnerable groups of population, trials of healthy volunteers, ethical issues of medical technology assessment are described.

A separate chapter is devoted to ethnocultural and confessional peculiarities of biomedical trials. It is known that sociocultural environment plays an important role while planning biomedical research. It is about selection of both the trial subjects, and members of the study personnel. Ignoring sociocultural peculiarities at all trial stages is a typical mistake. Taking into account ethnocultural and confessional components of biomedical research helps avoiding stress among subjects and violation of human rights during biomedical trials.

A specific nature of the projects associated with biobanks, use of gene therapy and biomedical cellular products, tissue engineering preparations, artificial intelligence software, robotic medical complexes, 3D-bioprinting, use of medical devices with the Internet of Bodies, and translational research has been shown. The types of biomedical trials are reviewed. Recommendations are provided concerning proper organization of an ethical examination amidst the pandemic and emergency situations.

Separate chapters are devoted to an ethical examination of medical devices, animal trials and translational trials.

CONCLUSION

There are many current concerns about an adequate, timely, scientifically grounded, independent review of high technologies due to the increasingly active development and implementation of biological and information technologies into a significant number of both new, and traditional, long-established groups of public relations, necessity in getting the balance of interests, including citizens, businesses, social groups, and the state.

That's why the issue about development and adoption of a set of standards that mediate relations associated with ethical and legal support, support of newly forming technological reality (arising and developing at the interface of general humanitarian, sociocultural, technological, biological, medical and other disciplines) has been discussed in increasing frequency.

The guideline is intended for daily use by ethics committee members during an expert assessment of biomedical trials; specialists engaged in the trials; those who are busy in clinics, pharmaceutical companies, contract research organizations, supervisors of scientific and clinical projects, representatives of regulating bodies, research and development establishments, and higher attestation commissions.

The presented information is useful for research associates and postgraduates who are planning to begin or have already begun conducting biomedical trials in accordance with international requirements. The guideline can also be used to develop basic training courses devoted to biomedical ethics in higher educational facilities; it is also suitable for teachers while planning and conducting training sessions. Experienced specialists such as ethics committee members and clinical investigators can use the presented information to broaden their horizons, improve the scientific part, supplement legal knowledge, understand the methodology of various biomedical trials in accordance with international standards and modern ethical principles.

Considering the importance, novelty and practical significance of the issues reviewed, it can be concluded that 'Ethical Examination in Biomedical Research: Practical Considerations for Ethics Committees under the general editorship of Khokhlov AL' will make a huge contribution into bioethics development in Russia and in functioning of ethics committees during improvement of an ethical examination, in particular.

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PHYSICIAN-PATIENT RELATIONSHIP IN DERMATOLOGY: SPECIFICITY OF ETHICAL ISSUES

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The article deals with ethical aspects of physician-patient relationship in dermatology, and demonstrates their influence on success of diagnostic and treatment activities and level of satisfaction with quality of medical services. Special attention is paid to the specific nature of bioethical issues in dermatology, associated with visuality and peculiarities of the course of disease, emotional and physiological background and coexisting disorders. Special priority is given to effective strategies of physician-patient communication, respect for patient autonomy and protection of confidentiality both in clinical practice, and on the Internet. It is shown that linking personal and strategic social media accounts raises a number of ethical and legal issues, associated with obtaining voluntary informed consent, compliance with standards of corporate ethics, and perception of medical information by non-professional audience. In conclusion, compliance with principles and rules of biomedical ethics is important to set constructive relations in clinical dermatological practice, ensure social trust in medicine and prepare future specialists. It is also important to discuss ethical issues in a professional community, slowly forming an interdisciplinary space of communication between physicians, health officials, specialists in bioethics, medical law, psychology and sociology of medicine.

Key words: dermatology, bioethics, physician-patient relationship, intimate space of the patient, social networks

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ВЗАИМООТНОШЕНИЯ ВРАЧ-ПАЦИЕНТ В ДЕРМАТОЛОГИИ: СПЕЦИФИКА ЭТИЧЕСКИХ ПРОБЛЕМ

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В статье рассматриваются этические аспекты взаимоотношений врач-пациент в дерматологии, показано их влияние на успех лечебно-диагностических мероприятий и степень удовлетворенности качеством медицинских услуг. Акцентируется внимание на специфике биоэтических проблем дерматологии, обусловленных визуальностью и особенностями течения заболеваний, эмоционально-психологическим фоном и сопутствующими заболеваниями пациента. Особое внимание также уделено эффективным коммуникативным стратегиям во взаимодействии врача с пациентом, необходимости уважения автономии пациента и защиты конфиденциальности как в непосредственной клинической практике, так и в Интернет-пространстве. Показано, что совмещение врачами персонального и контент-стратегического аккаунтов в социальных сетях поднимает ряд этико-правовых вопросов, связанных с добровольным информированным согласием, соблюдением норм корпоративный этики, восприятием медицинского материала непрофессиональной аудиторией. В заключение отмечается, что соблюдение принципов и правил биомедицинской этики важно для установления конструктивных отношений в клинической практике в дерматологии, для социального доверия медицине и подготовки будущих специалистов. Вместе с тем необходимо обсуждать вопросы этики в профессиональном сообществе, постепенно формируя междисциплинарное пространство диалога врачей, организаторов здравоохранения, специалистов в области биоэтики, медицинского права, психологии и социологии медицины.

Ключевые слова: дерматология, биоэтика, взаимоотношения врач-пациент, интимное пространство пациента, социальные сети

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Ethical aspects of physician-patient relationship produce a significant influence on patients' readiness to communicate with a doctor and their adherence to treatment, success of therapeutic and diagnostic activities and level of satisfaction with the quality of medical services. Every area of medicine has inherent characteristics associated with moral aspects of doctor-patient communication. In dermatology, it is due to visuality and peculiarities of disease course, emotional and psychological background and concurrent diseases. Meanwhile, issues about necessary and accessible borders of intervention in the intimate zone of a patient, preferrable communication strategies, ways to respect autonomy and protect confidentiality arise not in direct clinical practice only, but also on the Internet, where doctors and patients exchange data, share opinions and experience, discuss own and other experience.

SPECIFIC NATURE OF DERMATOLOGY: BIOETHICAL ASPECTS

Just like any area of medicine, dermatology has its own peculiarities. They are associated with frequent chronization, chronic diseases and long-term doctor-patient relationships, visuality of clinical manifestations that constantly remind a patient of esthetic shortcomings related to the issues of self-perception and interaction with other people. Psychosocial disease consequences are as discomfortable as direct clinical

manifestations. That's why while estimating the disease severity, it is required to take into account not only 'the medical' complaints, but also the possible severity of concurrent psychoemotional feelings of a patient.

Thus, from a medical point of view, not the worst skin disease (Acne vulgaris) can result in suicide as severe depression is developed. People can't accept their appearance or cope with collective bullying. It is not accidental that previous models of doctor-patient relationships are substituted with patient-centered interaction strategies where a doctor's communication competency is important. A doctor must be able to ensure effective communication with a patient, listen to the patient and understand him/her, take into account non-verbal signs. Thus, a patient-centered approach and the corresponding mental atmosphere make it possible to estimate both objective signs of a disease, and dangers and expectations of a person, achieve shared understanding of a problem, and agree upon a plan of subsequent examination and treatment.

At the same time, patient centricity means to maintain communication boundaries, protect personal space and ensure certain emotional neutrality of the parties involved. An ability to feel empathy (emotional empathy), a doctor's ability to constant communication (empathic care) and cognitive empathy are considered equivalent to virtues. Can hyper-empathy produce a negative influence and turn a therapeutic process into close or compulsive relationships? Which consequences can arise when formal communication is turned to non-formal one?

When answering the questions, it's necessary to consider the image of a dermatologist. Long-term and emotionally-colored doctor-patient relationships and a doctor's mistakes while establishing the rules of communication can result in erroneous understanding of relations as appropriately close, searches for consultations with relatives, friends, colleagues by correspondence, attempts to communicate with a doctor outside of working hours or during vacation. Besides, this can lead to distant consultations and distribution of a doctor's contacts without permission of the latter when a patient finds it useless or is unwilling to fix an appointment or spend time on an in-person visit.

It is not a secret that social networks are highly important both for the medical society, and for the citizens with common interests in health issues. This is a convenient tool to exchange experience and opinions, provide mutual aid, and widely distribute data about medical organizations or certain specialists. According to the US-based research, 81% of adults had social profiles; almost 1/3 of consumer activity associated with health issues run through social networks; about 2/3 of consumers searched for a medical representative using social media as well [1].

Based on another review, almost half of Internet users accepted that social networks influence their subsequent decisions related to health issues; over half of those surveyed expressed confidence in publications and blogs of doctors on the Internet [2].

Based on medical content analysis of texts of one of the most popular Russian social network (VKontakte), the most popular topics assessed and discussed include healthcare professionals, their activity and clinics, whereas patients are very rarely discussed [3]. When a patient pressed a 'Like' button to assess publications of his friend dermatologist who consequently ignored him and didn't provide feedback or didn't make an appointment, the unsatisfied patient could probably leave an open abusive comment or a vicious remark that could influence the doctor's reputation.

In this context, it's important to consider the accessibility of a doctor's personal data in social media. It is mainly due to linking of personal and strategic accounts because of clear reasons such as attraction of new patients to a clinic, expansion of the target audience, increased trust of subscribers, improved level of income and development of an expert image using a certain nosology.

Dermatologists and cosmetologists often publish in one click photos and videos 'before, during and after' or 'share own opinion' to demonstrate their professionalism. But they don't always analyze ethical issues of submitting information to a wide lay audience and legality of their actions. Even if a patient expresses his or her consent to make and subsequently distribute health-related photos/videos orally or in writing, there are still obvious doubts. A patient can wonder whether the doctor always observes the conditions of consent obtaining; what guarantees can be given about non-distribution of the patient's body images; whether the photos or videos can enter other Internet platforms without the patient's consent.

Growing availability of online libraries with digital images of high quality and archival photos and videos posted by dermatologists and cosmetologists in social media is definitely of educational value. At the same time there is a possibility that medical information can be misused, for instance, with the purpose of searching for and distributing sexual images, including pornography.

Thus, DermAtlas (the largest open repository of highly qualitative clinical and histological images in dermatology) can be accessed via a search system using various criteria. Analysis of 3,664,191 queries of users from October 2004 to March 2005 has shown that seven body sites out of 10 were most commonly searched for. 10,307 analyzed queries simultaneously included body sites and age: 'genital area' for 33.4% of users, and 'children' for 72.6% of users [4].

Thus, justifiable doubts arise about a proper use of DermAtlas online library image database and other photos and videos on professional dermatology sites, as they undermine confidence in confidentiality of information related to those patients who gave their consent to the use of photos and personal data for educational purposes.

COMORBIDITY AND POLYMORBIDITY IN DERMATOLOGY: MORAL MEASUREMENTS

Comorbidity and polymorbidity (when a patient has not only skin diseases, but also one or several disturbances that coincide in time or are interconnected with single pathogenetic mechanisms) belong to another peculiarity of a dermatologist's clinical practice. According to some authors, one-third of a dermatologist's patients have comorbid mental disorders (psychophysiological dermatoses, stress-reactive dermatoses) of various intensity [5]. This influences the type of doctor-patient relationship and sometimes requires participation of a psychotherapist or psychiatrist in treatment of dermatology patients, developing the model of 'integrative medicine'. Urgency of the issue confirms active development of psychodermatology used by doctors to build functional relations with patients, obtain optimal results of treatment and rehabilitation [6].

Dermatological nosologies are often associated with gastrointestinal diseases, infectious and inflammatory or allergic respiratory diseases, endocrine and metabolic disturbances. They require interdisciplinary interaction. Thus, occurrence of the combined pathology makes up to 69% among patients aged 18 to 44; up to 93% among those aged 45 to 64; and up to 98% among those elder than 65 [7]. Many patients simultaneously see three or even more doctors. According to Russian bioethics T. D. Tishchenko, 'while trying to solve the

problems of their suffering *flesh'*, patients move from one doctor to another one, *uniting* disciplinary and institutionally isolated medical practices in more or less effective network structures. Their *flesh* dissected into a variety of *bodies* under the faceted disciplinary stare of doctors is healing (acquires a rationed linkage) in the biographical route of a certain patient' [8].

In the future, medicine will probably get away from the disciplinary separation of the 'suffering flesh'. However, the current common practice is represented by a nosological approach to diagnostics and treatment. The approach doesn't always ensure therapeutic success and satisfaction of people with the obtained aid. Doesn't a doctor face such a complex ethical issue as taking the responsibility for grouping isolated consultations into the single system of aid considering a patient-centered approach?

LIMITS OF CONFIDENCE AND INTIMATE PART OF DERMATOLOGICAL EXAMINATION

Dermatologist-patient interrelation often includes an intimate examination, tactile interaction, delicate interrogations and dialogues. This sometimes causes difficulties associated with age- and gender-related shyness, and can threaten with disturbances of sexual boundaries both on the part of a doctor, and on the part of a patient. Disturbed sexual boundaries include not only obvious cases of entering (or wishing to enter) into sexual relations with a patient irrespective of the will of the latter. In certain cases, an unsound medical examination can be treated as sexual violence or abuse. Besides, cases of sexual boundary violations can also involve sexual comments, including indecent humor or hints, affected manners, sexually touching patients, use of words or actions that can be reasonably interpreted as the ones intended for excitation or satisfaction of a sexual wish, asking patients about their sexual history or preferences that have no relation to medical service without giving an explanation why the issues must be discussed. Finally, asking a patient to remove more clothes than it is necessary can be taken as violation of allowable boundaries.

Doctors carry full responsibility for establishing and maintaining sexual boundaries with their patients [9]. In these relations, sexual contacts by mutual agreement and comments or undue behavior associated with sexual abuse are inacceptable.

Tense situations faced during a consultation with a dermatologist when a patient or a doctor can feel extremely uneasy or be emotional over violation of sexual boundaries include a medical examination. It is especially true about an intimate examination, the stressogenicity of which can pose a serious problem both for a doctor, and a patient. An intimate examination is an examination and palpation of mammary glands, external examination of the genital area or internal examination (vaginal or rectal). In the interview, the students of the Faculty of Medical Sciences from Newcastle University (Great Britain) reported bigger mental discomfort during an intimate examination of young patients as compared with the elderly, and a greater stress during an examination in patients of the opposite sex. Some students described their attitude to an intimate examination as something that needed 'to be done as quickly as possible', failed to use some research methods to decrease a patient's discomfort or stress, and mentioned that the greatest inconvenience was experienced when male students were examining female patients [10].

It must be noted that limited time spent on learning techniques and conditions of a patient's intimate examination (role modeling of clinical situations, use of imitation models, theoretical literacy) during the process of a doctor's preparation results in insufficient competence of a young specialist in real clinical conditions and can involve direct (physical trauma) and indirect (insufficient examination, mental stress) harm to a patient.

Religious context, upbringing traditions, social status and education can influence the ideas of intimacy and must be taken into account. Being diplomatic and showing respect for a patient's opinion when discussing the necessity in an intimate examination ensure comfort, improve trust in doctors and increase effectiveness of the subsequent therapeutic and diagnostic process. Considering delicacy of an intimate examination and investigation, a dermatovenerologist needs to take into account the following rules:

- present a plan and sequence of a physical examination in simple words, explain the necessity in certain manipulations, use of certain instruments, give a patient a chance to ask questions or refuse from an examination;
- obtain informed consent to an intimate examination;
- obtain written consent of a patient to the presence of students or another third person during an examination or consultation. It should also be taken into consideration that an unsound medical examination performed without a proper execution of medical documentation and clinical substantiation can be taken as a form of sexual abuse;
- provide for comfortable mental and technical conditions to prepare a patient for an intimate examination (removal of/putting on clothes without an external observation, minimum of time spent by the naked patient outside the procedure; closing the door or windows, if any). A doctor needs to avoid helping a patient to remove/put on the clothes except for the cases when the patient has difficulties in doing so and asks for help;
- to ensure additional comfort during a consultation owing to the presence of a third person who supports the patient and if the patient gives such consent or requests so. Many specialists believe that the presence of a third person who witnesses the consultation should be useful. These can be doctors and nurses, a parent, caretaker, spouse, family member. The observer must understand the function fulfilled on the part of a patient, be a person acceptable for the patient, respect the patient's private life and dignity, and keep confidentiality. At the same time, a patient has a right to refuse the attendance of a third person. In this case, a doctor needs to take a decision whether he/she is ready to continue a consultation in the absence of the third person.

An examination needs to be carried out with a certain hint of delicacy including:

- supervision of a patient: any verbal or non-verbal sign can mean that a patient wants to withdraw a consent to the examination;
- exclusion of side conversations in an examination room when a patient is getting ready for an examination (both face-to-face and by phone), any use of mobile devices (opening applications, printing text messages), telling indecent or ambiguous jokes, inappropriate discussion of other patients or telling 'funny' stories occurred during a previous physical examination;
- obvious for a patient decontamination of hands while getting ready for an examination of the genital area, mammary glands, internal examination and after a physical examination (washing hands, removal of jewelry that prevents proper hygienic procedures, use of antiseptic external means, obligatory use of examination gloves). Examination gloves are required not only to

protect the hands of a dermatologist, but also to create a barrier during tactile interaction as they keep heat transfer and subjective sensations of touching the skin or mucous to a minimum.

Another problematic issue in medical practice includes the issue of consultation surveillance and video protocolling right at a doctor's office, both at the initiative of a medical preventive institution (MPI), and as desired by a patient. According to Government regulation as of January 13, 2019 No. 8 and part 13 of art. 30 of FL as of December 30, 2009 No. 384, MPI administration must conduct surveillance of the situation in the entire MPI, archive and store data during 30 days in order to withstand terrorism and illegal actions, and protect visitors and personnel. However, is it possible to compare significance of video monitoring in common areas of a medical organization, an operating room or a special care ward with video surveillance in a diagnostic room of a dermatovenerologist?

On the one hand, video surveillance can be good for medical personnel and administration of an MPI, as it allows to analyze the doctor-patient interaction model, timely and properly react to disputable situations or complaints of a patient, and to improve a doctor's communication skills. This is also associated with certain risks of confidentiality disturbances as the images of a face or body parts of a patient or a doctor, and voice recording represent personal data protected at the level of the federal legislation.

Besides, more data have appeared lately about unauthorized (hidden) or direct video- or audio recording of a doctor's appointment by patients. This happens because a consumer of medical services doesn't understand or poorly remembers information provided at a doctor's office and wants to listen to the data later as many times as it is necessary to collect material for possible subsequent public use or document a claim against the MPI. Which instruments are at a dermatologist's disposal to prevent illegal collection and distribution of personal data? Can videorecording of the consultative and diagnostic process performed without a doctor's consent be a sound argument for premature termination of an appointment and denying medical services to a patient?

CONCLUSION

Thus, both doctor-patient communication in clinical practice, and exchange of medical data and experience on different Internet resources are connected to a set of ethical standards and issues. It is essential to follow the principles and rules of biomedical ethics to establish positive and good relations in clinical dermatological practice, to express social trust in medicine and for professional preparation of future specialists. It is also necessary to discuss ethical issues in a professional community, slowly forming an interdisciplinary space of communication between physicians, health officials, specialists in bioethics, medical law, psychology and sociology of medicine to search for reactions to complicated moral challenges of modern biomedicine.

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FUSION OF ANCIENT PHILOSOPHY AND ART OF MEDICAL SCIENCE IN THE MAKING OF BASICS OF MEDICAL ETHICS

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In the modern world, a human being comes across the double absolute priority given to the values of medical ethics. On the one hand, moral ideals are metaphysical by nature. On the other hand, a human being treats ethical standards of medical ethics pragmatically. In this aspect, the key players of the ancient world who developed the metaphysical basics of medical ethics were especially important. The study is aimed at determining the contribution of ancient thinkers into development of fundamental basics of medical ethics. The works of ancient thinkers were taken as materials for the study. The study methods are represented by system analysis, dialectic method, phenomenological and hermeneutical approaches that enable to interpret the ideas of thinkers in relation to creating the basics of medical ethics. It has been established during the study that thinking based on the integration of rational, empirical and metaphysical principles has been developed in the ancient world. Metaphysical provisions of Plato and Aristotle manifested through the works of Galen make it is possible to conclude on eclectic philosophical views of Claudius Galen. Eclecticism is not just about plain borrowing of ideas, but about new fusion of physics, logics, and metaphysics in relation to understanding human health and disease. It can be stated that the first stage of nature cognition (natural philosophy) is the most important stage of developing sense-making basics of medical ethics. This period turns into a starting point for the emerging basics of fused humanitarian and natural science-based knowledge and formation of medical ethics principles.

Key words: metaphysics, medical ethics, culture, natural science, humanitarian sciences, medicine, culturological values, civilization, humanism

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СИНТЕЗ АНТИЧНОЙ ФИЛОСОФИИ И ВРАЧЕБНОГО ИСКУССТВА В ПРОЦЕССЕ СТАНОВЛЕНИЯ ОСНОВ МЕДИЦИНСКОЙ ЭТИКИ

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В современных условиях человек сталкивается с двойной абсолютизацией ценностей медицинской этики. С одной стороны, моральные идеалы носят метафизический характер. С другой — этические нормы медицинской этики предстают перед человеком в прагматическом смысле. В этом плане представляется особенно важным рассмотрение ключевых фигур античности, предпринявших формирование метафизических основ медицинской этики. Цель исследования — определение вклада мыслителей античности в развитие фундаментальных основ медицинской этики. Материалом для исследования послужили работы мыслителей античности. Методами исследования являются системный анализ, диалектический метод, феноменологический и герменевтический подходы, позволяющие интерпретировать идеи мыслителей применительно к созданию основ медицинской этики. В результате исследования установлено, что именно в античности формировалось мышление, основанное на интеграции рациональных, эмпирических и метафизических принципов. Метафизические положения Платона и Аристотеля, проявившиеся у Галена, позволяют сделать вывод об эклектичности философских взглядов Клавдия Галена. Но эта эклектичность есть не простое заимствование идей, а новый синтез физики, логики, метафизики применительно к пониманию здоровья и болезни человека. Можно установить, что первая стадия познания природы — натурфилософия — является важнейшей фазой формирования смыслообразующих основ медицинской этики. Именно этот период становится отправной точкой для наметившихся основ синтеза гуманитарного и естественно-научного знания, а также формирования принципов медицинской этики.

Ключевые слова: метафизика, медицинская этика, культура, естествознание, гуманитарные науки, медицина, культурологические ценности, цивилизация, гуманизм

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In the modern world, a human being comes across the double absolute priority given to the values of medical ethics. On the one hand, moral ideals are metaphysical. On the other hand, a human being treats ethical standards of medical ethics pragmatically, as certain guarantors of happy existence. Meanwhile, in the system of natural science, a modern person prioritizes pragmatic values.

Steady growth of scientific and technical problems in the modern society results in reconsideration of the entire system of natural science. General scientific reflection is necessary. Natural science is gradually becoming a center that integrates all aspects of reality. In this regard, it is especially important to deal with the key personality of early natural science development history represented by a thinker, doctor and philosopher Claudius Galen.

When Galen's art of medical science was developing, the Roman epoch was characterized by overlapping of two polar concepts. They included the materialistic understanding of nature and humans, and the idealistic approach based on mysticism and mythological world view leftovers. Many scientists failed to avoid the duality. However, Claudius Galen can serve as an example of creative overcoming the duality through breaking the tendencies in his art.

It should be noted that D. A. Balalykin, editor of Galen's works, made a significant contribution into the study of the philosopher's artistic legacy. He wrote commentary to Galen's collected works, and a number of works on history of medicine [1, 2]. He considers various approaches to different directions of a medical thought to treatment practice [2].

During this period, naturalistic tendencies in medicine prevailed. N. P. Shock mentioned that the search for cause-and-effect relations produced in the course of treatment was done by Galen based on his knowledge of math, logics and astronomy [3]. Medieval perception of 'Divine Galen' has survived to the present day. There is no doubt that Galen's contemporaries admired the creative genius of Galen. Marcus Aurelius, under whose reign an important part of Galen's creativity was implemented, couldn't help noticing the philosopher's merits and contribution to medicine. In his twelfth book 'Alone to Myself' Marcus Aurelius, who was impressed by Galen's ideas, wrote as follows: 'Think of the condition of your body and soul when death comes, of life brevity, yawning abyss of eternity behind and in front of you, powerlessness of material things' [4, p. 801]. Here he speculates over the ratio of materialistic and ideal fundamentals. It is the duality typical of Galen.

The thesis can mean nothing to a modern human, as pragmatic values of modern medical ethics exclude the possibility of thinking about metaphysical issues of eternity, death and impossibility to withstand the thinking categories. The individual practically assumes that thinking can distinguish between the world properties that depend on the attitude to reality, and the world to one's self that continues its existence irrespective of an observer.

Marcus Tullius Cicero, being a follower of Plato, reflected an interaction of idealistic and materialistic tendencies in his creative work. In his book 'On Obligations' he writes as follows: '… if we treat nature as a supervisor, we'll never make an error and will follow the beginning which is delicate and distinctive by nature, and the beginning that corresponds to the requirements of a human society…' [4, p. 287]. Cicero developed an idea of subjugation of all passions and aspiration by reason. It is a cognitive ability that makes humans different from animals.

The opinion is controversial. When a human thinks of a property that belongs to the entire world, an individual enters the endless circle of reasoning. A human thinks of a certain world property as an act of thinking. Thus, the values of medical ethics can be only imaginable. Their implementation in the world depends on a human will only. The transcendental nature of values of medical ethics is essentially denied here.

Claudius Galen was familiar with Plato's works, attached much significance to Aristotle's works, valued the merits of Stoic and Epicurean. He started studying philosophy when he was 14 years old, and referred to medicine at the age of 17. He visited many cities such as Alexandria, Athene, Corinth and Smyrna to improve his knowledge. The thinker examined the works by Aristotle and found many interesting data there. It's the logics by Aristotle that was fundamental when Galen's method was developed. A. P. Shcheglov determines Galen's method and calls it reduction of theoretical and logical assumptions to practical acts. He mentions an essential value of Aristotle's works in formation of Galen's method [5].

In this regard, it is necessary to point at falseness of the thesis. Aristotle mentioned that medical treatment must rest upon metaphysical entities. The main thing for Aristotle is to know the reason for the disease. This is followed by empirical experience. Thus, according to Aristotle, a doctor's wisdom means to know the patterns of metaphysical reality, which includes understanding not only the reasons for a disease, but also ethical values, which are mandatory for doctors. He noticed that sciences about 'something ideological' are beyond the arts of creation. Aristotle shows the priority of ethical values in the art of medical science, their metaphysical nature.

Galen had been improving his skills for a long time, treating gladiators. Only in 164 Galen moved to Rome, where he served Marcus Aurelius. Galen didn't only improve his medical practice, but also submerged deep into research activities, performed an autopsy on animals, delivered lectures. During that time, Galen examined physiology of animals and tried to use the obtained knowledge when studying the structure of human organs.

Historically, Hippocrates was Galen's idol. Galen took a diseased condition of a human within Hippocrates' theory of the four humors. That's why regular mixing of humors such as blood, phlegm, yellow bile, and black bile (isonomia) preserves balance and corresponds to the term of 'health'. However, prevalence of one of the humors (monarhia) is the reason for the disease. Galen estimated the disease in a materialistic way and was rational to some extent. According to his ideas, a disease is a special state of an organism with the disturbed functioning of separate organs and parts of the body. We see a lack of mysticism typical of the ancient epoch, when people believed that diseases were sent by gods. According to Galen, diseases occurred due to heat excess or plentiful supply or shortage of food. The factors were definitely of materialistic nature and could disturb the functioning of certain organs. Galen initiated the study of disease symptoms based on the union of external and internal factors that influence health. Thus, he stressed the significance of medicines and diet when justifying his own clinical method.

Similar thoughts can be found in Hippocrates' 'On the Sacred Disease'. He wrote as follows: '… if all this used as clothes and taken as food results in the birth and spread of a disease, and if a disease can be avoided with the help of dietary restraint, it's not a god or religious purification that are the helping reasons; but what is eaten can cure or do harm, whereas god's influence has nothing to do with it' [6, p. 209].

However, we can see that discovery of symptoms as principal medical categories makes transition to metaphysical entities obvious in Galen's work. Both Hippocrates, and Galen tried to understand the basics of medical ethics, excluding the figure of God. Thus, God has no power to heal a person. The healing problem is interpreted as the problem when a human achieves harmony with himself (metaphysical basis) and as a benefit of a healthy human to the society (pragmatic basis). Metaphysical basis was of the highest priority during formation and development of medical ethics.

When creating his method, Galen was under the influence of Anaximenes. Galen used the doctrine of air that can get condensed resulting in formation of clouds, water, snow and ice, and transferred this to a human body. That's why dry and warm are opposed to humid and cold. Though being primitive, the dialectics of the polarities was borrowed from Heraclites. Hippocrates' thesis stating that 'opposites are cured by opposites' made sense in Galen's practice as well.

Study of anatomy helped Galen introduce significant changes into the ideas of a human body. He denied existence of 'pneuma' in human arteries, as they were filled with blood. Lucretius wrote about blood in the arteries in his poem 'On the Nature of Things'.

> 'It is clearly stated where something should be and where it should be developed.
> So the soul by nature cannot exist alone without body and apart from muscles and blood' [4, p. 83].

In his book 'Tusculan Disputations', Cicero echoed Lucretius about the bond/differences between the body and the soul. He stated that a healthy soul could 'be influenced by the body, but not by the disease' [7, p. 328]. Cicero concluded that a disease was not always the fault of a body, but when the soul suffered, it was to be blamed. Thus, moral basis must be primarily understood concerning the landmarks of human existence, that can be provided by medical ethics.

Galen considered that pneuma moved not through the arteries (according to previous thinkers), but through the veins. Galen treated pneuma in a different way. He differentiated between the following types of pneuma: spiritual for the brain (Spiritus animalis); vital for the heart (Spiritus vitalis); and natural for the liver (Spiritus naturalis).

Galen had liver for the main as compared with the soul: 'As the craving part of the soul is embraced in the liver, which is the third internal organ, a human who intends to create a perfect order in his soul must have a symmetry of inherent movements' [8, p. 351]. Galen stresses the priority of metaphysical cognition over the sensual experience, as the liver is responsible for sufferings of an individual in this empirical world.

Three types of pneuma correspond to three origins of a human soul described in Plato's Republic. The three parts of the soul are the rational, spirited and appetitive parts. The third one is called 'appetitive because of unusual lust for food, drinking, and romantic episodes…' [9, p. 383]. In this respect, Galen's spiritual pneuma corresponds to cognition of metaphysical entities, i. e. moral basis, which is similar to Plato's rational beginning. The spirited pneuma is similar to Plato's second beginning. The life pneuma is the same as Plato's appetitive soul part. Thus, we see than Galen, just like Plato, prioritizes the value of metaphysical basis in formation of medical ethics.

By developing the doctrine of pneuma, Galen was influenced by Aristotle. Galen believed that a human birth was associated with 'the rational pneuma'. Air, breathed in by a human, touches it and carries the 'primary pneuma'. According to Galen, the heart was an organ that processed air: 'Heartbeat and concentration of the entire soul in this place belongs to an evident sign of fear' [8, p. 361]. Galen believed that the process resulted in formation of a new, 'animal pneuma' that controlled all the physiological processes of the body. Aristotle defined the process as 'blood boiling or heat near the heart' [10, p. 36]. Aristotle also noted that the reasons for the phenomena deserved cognition, as it were the consequences that were comprehended based on the reasons but not vice versa. According to Aristotle, the science that comprehended a purpose, this or that advantage, was the principal one. The idea of an advantage substantiated by ethical standards was the basics for medical ethics. In his opinion, the science was truly free, as it existed for itself. Thus, possession of medical ethics was put by Aristotle higher than human possibilities.

I. V. Prolygina states that Galen's medical knowledge can be characterized as fusion of empirical knowledge and logical thoughts resulting from Euclidian postulates and Aristotle's syllogisms [11].

It is true that Galen's pneuma doctrine can be characterized as some outbreak in understanding of physiological processes even in comparison with Aristotle's concept. Galen stressed the value of the brain, whereas Aristotle mentioned 'the soul movements only'. Galen considered a pneuma movement in the brain, stating that in the brain, pneuma was becoming even thinner turning into mental pneuma. According to Galen, pneuma was running through the nerves and brought impulses from the brain to the body periphery and back. In On the Soul tractate, Aristotle wrote as follows: 'when the surrounding air compresses bodies and displaces atoms that make living creatures move, because they are never still, protection occurs, other atoms that prevent liberation of atoms inside the living creatures enter the body from the outside… and living creatures stay alive until they are capable of it' [10, p. 40–41]. But these processes seem useless if a person stops believing in 'non-measurable'. In the end, Aristotle calls for 'the best', i. e. awareness of the form of the good. That's why the thinker states that the science that can be possessed by God is divine. According to Aristotle, all sciences including medicine are more necessary for people, but there is no science better than ethics.

Galen describes the nervous system functioning in a more rational way than Aristotle. However, Galen considers physiological processes in an idealistic way. Pneuma activity is a manifested transformation of certain spirits. Thus, Galen considers nerves as a manifestation of 'animal spirits' (Vis animalis), liver as a synthesizer of 'natural spirits' (Vis naturalis), and heart as pulsating spirits (Vis pulsitiva).

While trying to understand how the nervous system functions, Galen conducted many animal experiments. He even conducted the experiments during his public lectures. The thinker introduced many additions and changes into the experimental data that were available after Hippocrates. The level of understanding of how sensory organs function inherited by Galen can be found in the book by Diogen Laertski who writes as follows: '…they substantiate the existence of channels in sensory organs referring to the flow of objects; though the objects can be substantiated only when there are channels in sensory organs' [12, p. 461].

Diogen Laertski differentiates between two criteria of truth. The first criterion makes a decision. According to the thinker, this is the leading beginning of the soul. The second criterion means a clear and exact image used to make a decision. If a person rests upon images only, he will fail, as the images have no metaphysical basis and can be perceived by different people in a different way. A person who makes a decision should have a basic understanding of eternal and everlasting entities. Thus, we see how the rational basis of existence is transformed into metaphysical entities. The basics of medical ethics are formed using not a rational, but metaphysical basis.

Galen thoroughly examined muscular innervation by cutting the nerves reaching the glossopharyngeal muscles, extremities, facial muscles, diaphragm, intercostal muscles, etc. In this respect, Galen concludes that the motor ability directly depends on muscular tissue innervation. Demonstrating neutralization of nerves resulting in termination of sensation belonged to the most entertaining Galen's experiment. That was a sight of those times: for instance, experimental animals lost their voice: '…in neurotomy or ligature of all the mentioned nerves an animal is deprived of a voice, but breathes easily… it moves all the four extremities, can hear and see, preserving the entire depth of feelings' [8, p. 274]. These experiments made it possible for Galen to conclude that the nerves can be divided into three groups considering their functions. The first group included the nerves responsible for perception as they control the sensory organs. The second group included the nerves responsible for muscular activity. The nerves that regulated the functioning of internal organs belonged to the third group.

Thus, Galen's concept had not obvious hints, traits, and sketchy data enabling to see the basis that helped create a good theory of how the central nervous system is functioning, even in spite of the primitive development.

It is important to notice that Galen was the first of those who established an interaction between sensations and nervous activity. He found some areas in the brain which were

responsible for manifestations of thinking and sensations. Galen paid much attention to examination of the brain activity. He suggested that thinking was associated with the brain activity: 'the reasonable beginning from where nerves come are located in the brain' [8, p. 363]. S. Ya. Chikin notes that Galen destructs 'the myth of Aristotle', who believed that the brain cooled the warmth [13, p. 44]. However, in Metaphysics, Aristotle says that '…the mind is thinking independently as the subject of the thought was involved: it becomes the subject of the thought adhering to it and thinking that the mind and the subject are the same' [14, p. 364].

The fundamental conclusion about the thought and reality identity made by Aristotle makes us believe that a human being has such virtues as ethical values. According to Aristotle, medicine is becoming a creative science. Medical ethics is becoming fundamental here: 'good and beautiful are not the same (the first is always about the deed, whereas something beautiful is immobile)… [14, p. 389]. That's why medical ethics is becoming a dynamic science, as a doctor's acts must always correspond to the idea of the good, and formation of ethical standards is always the process of human development and perfection.

Claudius Galen considered, described and seriously examined various organs, systems, extremities of animals, and always compared the obtained data with the human body functioning. He stressed the importance of animal experiments: 'those saying that nerves are coming from the heart can say that and write about that just like they say and write about many other things; but they can't prove it during animal experiments' [8, p. 363]. Hence, we can conclude that Galen was not just an experimenter but also a theorist of medicine. This epoch lacked reasonable explanations of physiological phenomena, especially when it was attempted to confirm the conclusions in a practical way.

Galen tries to neutralize the contradiction between considering medicine as an art and understanding medicine as scientific work. Galen definitely treated medicine as science not forgetting Hippocrates reverence for the art of a doctor. A combination of these competing tendencies proves once again that there is a presence of combined rationalism and humanism in Galen's conception. 'A physician who is also a philosopher is similar to God' — the aphorism helps understand the reasons for Galen's creative work enormous success. In spite of Claudius Galen's inconsistent philosophy, his views point at materialistic tendencies in his creative work. Galen understood the complexity of medical knowledge development and progression, and advocated for introducing philosophy into medicine with medical ethics playing a leading role. The fundamentals of ethics enable a doctor to rise above the 'creeping' empirical practice and comprehend the reasons for diseases.

At the same time, Galen substantiated the use of empirical research methods. Observation was one of the most important methods. Empirical methods of treatment such as diet, gymnastics, bath, and massage are integrated into the humanistic concept of health and disease. A physician and a philosopher can't develop and comprehend the purposes and tasks of medical cognition without taking the methods into account.

First and foremost, Galen valued the statement of reasons as far as logical methods go. The method by Aristotle such as movement of a thought by analogy 'from alike to alike' was especially close to Galen. In Metaphysics, Aristotle wrote as follows: 'things are related when… what can make things hot is related to what can become hot, what can cut is related to what is cut… what is measurable is related to the measure, what is experienced is related to experience and what is conveyed by our senses is related to sensory perception' [14, p. 153].

Galen thoroughly examined Aristotle's philosophy. It's Aristotle's teleology that formed the basis of Galen's idea of expedient creations of nature. This allowed to formulate the fifth, i. e. 'instrumental' reason. It is notable that the statement by Aristotle 'nature does nothing in vain and misses nothing necessary' [10, p. 213] occupies a central position when developing Galen's scientific concept. This results in the following central conclusion: 'everything created by nature is excellent'. Thus, according to Galen, the divine idea of beauty is an initial point of considerations about goodness, whereas ethical standards belong to an indisputable condition of worthy curing.

The idea of beauty occupies one of the central ideas in Plato's philosophy. It allows to assume that Galen's gnoseology is formed based on Plato's idealism. In Feast, Plato considers the idea of beauty as a source of knowledge. Plato takes the idea as the basis for cognition of truth: '…only he alone, who was contemplating beauty… could give birth not the images of virtue, as he would not touch an image, but something true, as he would touch the truth' [15, p. 345]. Plato substantiates the true form of the good as the main idea that is crowning the entire pantheon of ideas. That's why ethical standards acquire a metaphysical character, even in Plato.

Plato's and Aristotle's metaphysical provisions manifested through Galen allow for the conclusion about Galen's eclectic philosophical views. But the eclecticism is not a plain borrowing of ideas, but a new fusion of physics, logics, metaphysics concerning understanding of human health and disease.

Galen's gnoseology absorbed integrative tendencies. The idea of spirituality of all living creatures is one tendency. The other tendency considers internal and external material reasons that influence health: '…all… diseases occur due to external reasons or reasons inside the body' [16, p. 663]. Galen's similar positions can seem contradicting. However, the contradiction is removed when a person is examined. On the one hand, the thinker criticizes representatives of 'creeping empirism' who rejected the purpose and divine participation in human creation. On the other hand, he disproves the opinion that creation of every body part pursues a certain purpose. Galen concludes that the mind was the reason why a human being mastered many arts. He wrote that a human being is the wisest of all living creatures, because he/she has hands. Due to similar ideas, Galen can be defined as Darwinism predecessor.

Claudius Galen surpassed all his contemporaries with the depth of a thought because he was able to establish the causal relation between the phenomena and detect the basis of functioning of all sides of reality. He established a connection between the structure of organs and their functions, and dependence between the body and a view of life. That's why Galen can be recognized as one of the first thinkers who was looking for and managed to find the rationale for integration of science and humanitarian knowledge.

Thus, it's necessary to point out Galen's ability for fusion of the knowledge obtained, his ability to summarize the experimental data, carry out philosophical analysis of medical problems and their integration into the general concept of human health. That's why the concept of Galen, and many other ancient philosophers, can serve as a starting point of setting the basics of medical ethics.

'A real doctor is always a philosopher' [17, p. 106]. This is the testament left by Galen to his descendants. It's the philosopher who can find the general foundation that allows to systematize all studied phenomena, formulate laws used to

create abnormal phenomena. Galen's classification of diseases is based on understanding of an anatomical substrate such as tissues, organs, elementary humors. In this respect, health absolute priority as the basic value in a human life characterizes Galen as a person of high moral character. In theory of medicine, the thinker overemphasized the notion of a standard, and considered an abnormality as a temporary phenomenon. Galen brought the notion of a standard under control of ethical principles. Achievement of happiness by a human being is the basis that can be the true foundation of medical ethics.

When analyzing the principal symptoms, a doctor's thinking must be based on examination of a healthy body, anatomy and physiology. Galen tried to integrate the notion of a healthy person and healthy way of life into the system of a doctor's world view: 'the leading principle states that principle and minor properties of any internal organ must be taken as the starting point…' [8, p. 362].

Thus, Galen's career was so outstanding and fruitful that it determined the basics of medical world view until the Renaissance. He created the system of healing uniting anatomy, prevention of diseases and therapy. Galen is traditionally characterized as a creator of scientific medicine. The feature is refracted through metaphysical elements of creation of medical ethics. Galen's scientific world view is impossible without taking into account empirism, and metaphysics enriched with the principles of rationality.

It is true that the world view, based on the unity of empirical, rational and metaphysical principles, was defined as 'educational knowledge' by M. Sheller. In Forms of Knowledge and Education, Sheller wrote that 'the educational knowledge is insight acquired on one or several good, precise samples and included into the system of knowledge; the insight became a form and rules of gripping the categories of all accidental facts of the future experience with the same essence' [18, p. 87].

Determining the utmost limits of science and technology development was called 'savage thinking' by Paul Ricceur. In his idea, it was a strive for final systematization of knowledge, resulting in the choice between different ways of understanding the reality [19]. According to Ricceur, this would be absurd. He shows that 'an idea about a value of any method can't be taken separately from understanding the borders' [19, p. 43]. The borders are increasingly associated with the issue of developing 'an ecological production' related to reproduction of nature and the entire environment.

It is relevant to remember V. I. Vernadky's words which can be considered as a testament of the thinker to younger generations: 'Alive, bold and young spirit embraced the scientific thinking. The modern scientific world view is shaking, destructing and changing under its influence. Unexpected horizons are opening far away in front. An intense burst of human creativity is currently striving for them' [20, p. 415].

Thus, C. Galen outpaced its epoch due the level of his world view. He built scientific thinking based on the integration of rational, empirical and metaphysical principles. His activity anticipated many discoveries in the area of medicine of the Renaissance.

Considering this excurse into history of medicine, it can be established that the first stage of nature perception (natural philosophy) is very important to understand the sense-making basics of medical ethics. Though only the methods of observation prevailed here, experimental methods were not introduced into the research, and many conclusions were primarily based on assumptions, intuitive insights, it can be concluded that the period becomes a starting point for the emergent basis of fusion of humanitarian and scientific knowledge, and development of the basics of medical ethics.

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THE ISSUES OF CLASSIFICATION AND CHARACTERIZATION OF NEUROTROPIC AGENTS IN THE TREATMENT OF PATIENTS WITH CEREBROVASCULAR DISEASES

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In developed countries, mortality from cerebrovascular diseases (CVD) is about 12%, which is second only to mortality from cardiovascular diseases. In order to make treatment of CVD successful, a complex approach to the problem is required with compensation for cardiovascular diseases (atherosclerosis, arterial hypertension, rheological properties of blood, etc.), elimination of neurological and psychopathological syndromes, improvement of cerebral circulation and use of neurotropic agents. The use of neurotropic agents by a practicing physician is complicated due to the lack of a clear classification reflecting their position and significance in CVD treatment. It is suggested that taking into account the predominant mechanism of action targeting for a pathological process, neurotropic agents should be divided into 4 groups such as neuroprotectors, neurometabolics, nootropics and neurotrophic agents (direct activators of neutrophin synthesis in the brain). The last group is related to analogues of regulatory peptides and shares positive properties with medicinal agents from other groups: they have the properties of primary and secondary neuroprotectors, neurometabolics, and produce a positive effect on cognitive functions of a healthy and sick person. Heptapeptide Semax is a typical agent belonging to this group.

Keywords: cerebrovascular diseases, neurotropic agents, neuroprotectors, neurometabolics, nootropics, neurotrophic agents, semax.

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ПРОБЛЕМЫ КЛАССИФИКАЦИИ И ХАРАКТЕРИСТИКА НЕЙРОТРОПНЫХ СРЕДСТВ, ПРИМЕНЯЕМЫХ ДЛЯ ТЕРАПИИ НАРУШЕНИЙ МОЗГОВОГО КРОВООБРАЩЕНИЯ

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Смертность от цереброваскулярных заболеваний (ЦВЗ) в экономически развитых странах составляет около 12%, уступая лишь смертности от заболеваний сердца. Успешное лечение ЦВЗ предполагает комплексный подход к проблеме, учитывающий компенсацию сердечно-сосудистых нарушений (атеросклероз, артериальная гипертония, реологические свойства крови и др.), устранение неврологических и психопатологических синдромов, улучшение церебральной циркуляции и применение нейротропных средств. Для практического врача использование нейротропных средств осложняется отсутствием внятной классификации, отражающей их место и значимость в лечении ЦВЗ. Предложено и обосновано разделение нейротропных средств на четыре группы, исходя из преимущественного механизма воздействия на патологический процесс: нейропротекторы, нейрометаболики, ноотропы и нейротрофические средства (прямые активаторы синтеза нейротрофинов головного мозга). Препараты последней группы относятся к классу аналогов регуляторных пептидов и во многом объединяют положительные свойства лекарственных средств из остальных групп: они обладают свойствами первичных и вторичных нейротротекторов, нейрометаболиков и положительно влияют на когнитивные функции здорового и больного человека. Типичным представителем данной группы лекарственных средств является гептапептид семакс.

Ключевые слова: цереброваскулярные заболевания, нейротропные средства, нейропротекторы, нейрометаболики, ноотропы, нейротрофические средства, семакс

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The most important task of modern medicine deals with how to increase the length of a human life with simultaneous preservation of high physical and mental capacity. It is impossible to solve the task with no significant progress in treatment of nervous and primarily cerebrovascular diseases (CVD). In developed countries, CVD mortality constitutes about 12%, which is second only to mortality from cardiovascular diseases [1]. According to the National Medical Research Center for Therapy and Preventive Medicine, up to 25% of men and 39% of women in Russia die of cerebrovascular diseases

[2]. The most dangerous CVD include acute cerebrovascular diseases (ACVD): stroke is the second leading global cause of death, being the main reason for disability among adults, mental disability and age-associated decrease in cognitive capabilities [3–7]. Chronic cerebrovascular disease (CCVD) is one of the most widely spread syndromes in clinical neurology leading to structural and functional changes in white and gray matter along with neurodegenerative diseases of the brain. It is the basic cause of development of cognitive disturbances in 5–22% of the elderly [8].

Modern drug therapy of nervous diseases, including CVD, is pathogenetic. A doctor uses a medicinal agent to influence the principal links of disease pathogenesis, trying to interrupt its course. Treatment of a patient depends on dynamics of a pathological process: the used agents can be changed depending on the time from disease onset, its type and clinical picture [9,10]. In acute conditions associated with blood circulatory disturbances (stroke and TIA), the struggle against parabiotic dead-end cells (penumbra in stroke) is the most important one. A patient's life and a possible scope of neurological and cognitive deficiency depend on effectiveness of the conducted therapy [2,3,11]. The most significant activities in CCVD include support of a normal functional state of neurons, regulated activity of neuromediatory systems and decrease in apoptosis rate [10]. Insufficiently effective treatment of nervous diseases worsens the quality of life, decreases social and familial adaptation, increases mortality and reduces the length of life [13].

In order to make treatment of CVD successful, a complex approach to the problem is required with compensation for cardiovascular diseases (atherosclerosis, arterial hypertension, rheological properties of blood, etc.), elimination of neurological and psychopathological syndromes, improvement of cerebral circulation and use of neurotropic agents [14]. Neurotropic agents with at least one of three important neurotropic effects (mnestic, neuroprotective and neurometabolic) have occupied a leading position in pathogenetic pharmacotherapy of the CNS during the last two decades. They have various mechanisms of action, different points of application at the neural level and inadequate clinical effectiveness and tolerability, but, in the majority of cases, a qualitatively similar therapeutic effect (positive influence on dynamics of neurological and cognitive deficiency, general condition, working capacity, self-service, etc.) [15,16].

The issues of classification of neurotropic agents. As a rule, neurotropic agents applied in CVD therapy have not only a multicomponent but also a crossover nature of action. That's why there are so many synonyms such as neuroprotectors, neurometabolic agents, true and mixed nootropic agents, neurodynamic, neuroregulatory, neurotrophic, neuroanabolic or eutotropic agents, neurometabolic cerebroprotectors, cerebroactivators, etc. [15,17]. As the compounds have different chemical structures and mechanisms of action, a single consistent classification is difficult to compose [3,17]. The existing classifications are usually based on the structural difference between neurotropic agents (which is of theoretical interest only) or/and used by authors to reflect all more or less significant properties of the agents. That's why the classification systems are too complex to be applied in practical medicine [3,16,18].

At the same time classification signs and definitions of medicinal agent groups should be clear to a practicing physician and help the doctor treat patients and select the most suitable drug. To achieve the purpose, the classification of neurotropic agents must be based on the principle of 'the leading or determinant type of action'. The mechanism of action of any drug has a type of action determining its therapeutic effectiveness in a certain disease. It is also necessary to consider a possible presence of clinically significant additional types of action. In this case, one of the most important tasks of clinical drug classification needs to be fulfilled. It is about making the choice of agents for monotherapy and combined pharmacotherapy clearer and simpler. Working with medicinal agents from two different groups, a doctor must be sure that they are not only compatible, but also mutually increase a therapeutic activity by way of potentiation (more desirable) or combination. At the same time, just equal enumeration of different aspects of the agent mechanism of action can make a doctor take a wrong decision about the combination of drugs.

Taking into account the abovementioned requirements, we suggest that only 4 groups of medicinal agents such as neuroprotectors, neurometabolic agents, nootropics and neurotropics should be differentiated among neurotrophic agents used in clinical practice by now.

NEUROPROTECTORS

Neuroprotectors are medicinal agents that increase resistance of cerebral tissue to the damaging effects of various genesis. **The most important feature of their mechanism of action consists in interrupting a cascade of pathological reactions (primarily of hypoxic and ischemic genesis) that cause neuronal damage**; they are also used to treat neurological deficiency and cognitive disturbances [19].

A clinical and pharmacodynamic subclassification of neuroprotectors is provided. It is based on the influence of the agents on certain mechanisms of primary (ischemic cascade) and delayed death of neurons. By now, there exist four groups of medicinal agents such as glutamate antagonists and different modulatory areas of glutamate receptors; antioxidants; precursors of membrane phospholipids or membrane protectors; agents with a complex mechanism of action.

Glutamate antagonists and various modulatory areas of glutamate receptors [20,21]:

- direct NMDA-receptor agonists demonstrated a marked toxicity and their tests failed to be beyond the scope of the experiment;
- low-affinity direct NMDA-receptor agonists: remacemide;
- non-competitive NMDA-receptor antagonists: aptiganel (cerestat), acatinol memantin (memantin) is almost the only widely applied agent of this group;
- glutamate release inhibitors: lubelusol.

As glutamate and calcium excitotoxicity is one of the leading links of neuronal death pathogenesis, serious hopes were put upon the group of antiglutamate agents from the mid-1990s onwards supported by vast experimental data. However, in acute CNS pathology, clinical activity of the agents was highly modest [22].

Antioxidants: their basic function is to protect neuronal membranes from damage by free radicals [23]. From 1980s, antioxidants have been used in neurological practice. Their included ascorbic acid, vitamin E, ceruloplasmin, ubiquinone, emoxypine, olyphenum, etc. Their basic shortcoming is a weakly marked antioxidant activity requiring long-term administration in high doses.

Mexidol (INN — ethylmethylhydroxypyridine succinate; chemical rational name — 3-oxy-6-methyl-2 ethylpyridine succinate), salt of emoxypine (similar to pyridoxine) and succinic acid, is an antioxidant with a real activity. Exogenous

succinate poorly penetrates via biological membranes, whereas emoxypine makes the transport easier. Emoxypine determines an antioxidant activity of mexidol, whereas succinate defines its neurometabolic constituent [25].

Precursors of membrane phospholipids (membrane protectors): their basic therapeutic mechanism is represented by reparation of damaged membranes due to phosphatidylcholine synthesis [24,26]**:**

- citicoline (cytidine-5-diphosphocholine) is a mononucleotide, naturally occurring endogenous compound, which is an intermediate in the synthesis of phospholipids in cell membranes [24,27,28];
- choline alfoscerate (alpha-glycerylphosphorylcholine-choline, gliatilin) is precursor of acetylcholine and phosphatidylcholine. The agent contains 40.5% of metabolically protected (formed in the brain only) choline [19].

They can't become the leading agents to treat the pathology, considering the mechanism of action of antioxidants and membrane protectors (suppressed activity of free-radical oxidation and preservation of membrane functions) and pathogenesis of the main hypoxic-ischemic cerebral diseases (activation of lipid peroxidation and membrane damage occur at final stages of an ischemic cascade). They are the most effective when used in complex therapy.

Medicinal agents with a complex mechanism of action. They currently include **Gingko Biloba preparations** (Memoplant, Tanacan, Bilobil, etc.). In Europe, they use only ginkgo leaves as crude drugs to make extracts standardized by content of basic effective agents (EGb 761): ginkgolides A, B and C (6%), bilobalide A (about 3%), containing about 24% of flavone glycosides. The set of active ingredients determines polypotency of clinical effects. The mechanism of therapeutic action is associated with inhibited processes of free-radical oxidation; membrane protective action (inhibition of PLC); inhibition of cerebral edema, anti-inflammatory action and decreased intensity of apoptosis [29].

Description of neuroprotective agents often includes data on calcium channel blockers (CCB: nimodipine, cinnarizine, flunarizine, etc.) as calcium ions play an important role in pathogenesis of neuronal damage (calcium and glutamate excitotoxicity). However, all CCB used in clinical practice disturb the current of calcium ions only through L-type slow voltage-gated channels located primarily in smooth muscles (for instance, a vascular wall). Calcium and glutamate excitotoxicity is implemented in response to excitation of glutamate receptors. Then calcium is distributed inside a cell via a fast receptor-associated ion channel, not affected by CCB. A neuron also has slow calcium channels, but these are not L-type, but N- and T-type channels [30]. In CVD, anti-calcium agents prevent overload of smooth muscles with calcium ions, increasing arrival of blood to the affected area and improving neuron survival [30]. This was an indirect protective effect only.

NEUROMETABOLIC AGENTS

The leading factor preserving neuroganglian structures in ischemia and hypoxia is represented by support of stable cerebral blood flow, oxygenation and creating the conditions that activate oxygen and glucose uptake to enable the Krebs cycle. In damaged nerve cells, restitution (restorative) processes can occur only in case of proper functioning of intracellular redox processes. **The main mechanism of action of neurometabolic agents is the effect produced on the principal link of pathogenesis of nerve injury (energy deficiency).** Neurometabolic agents mainly exert an antihypoxic action.

Tissue hypoxia results in energy deficiency and lactic acidosis, thus, activating the ischemic cascade. Decreased energy deficiency prevents ischemic cascade or decreases activity of all the links [23,25,27].

Neurometabolic agents form a heterogenous group of medicinal agents with different mechanisms of action. They have a common ability to increase effectiveness of neuronal metabolism under difficult conditions (hypoxia, ischemia, oxidative stress, etc.). As glucose is almost the only energy substrate for a neuron, and stimulation of its arrival to a cell is an important component of rational pharmacotherapy of brain diseases, the majority of effective neurometabolic agents can stimulate oxygen or glucose consumption and uptake in full-scale ischemia and hypoxia.

Neurometabolic agents differ by origin and mechanism of action. Among them, the following groups of medicinal agents can be distinguished:

- Tissue hydrolysates
- Neurometabolic agents with a marked mnestic activity
- Intermediates of Krebs cycle
- Fatty acid oxidation inhibitors
- Respiratory chain natural components
- Artificial redox systems
- High-energy compounds

Tissue hydrolysates. Three tissue hydrolysates (Actovegin, Cortexin, Cerebrolysin) are used in Russian neurology practice. Other agents of the group (Cerebramin, Cerebrocurin) are not of practical importance. Actovegin is a hemoderivative derived from calf blood via dialysis and ultrafiltration. Cerebrolysine is hydrolysate extracted from porcine brain tissue. Cortexin is obtained from the cerebral cortex of cattle and pigs not elder than 12 months.

They all contain microelements, vitamins, aminoacids, various intermediates, oligopeptides (with molecular weight of no more than 10 kJ) in certain proportions and concentrations [27]. Tissue hydrolysates have multiple components, but oligopeptides are the principal active ingredients. They are responsible for the basic mechanism of action for this group such as high glucose utilization by neurons. It produces a positive effect on their survival in hypoxia and ischemia, improves effectiveness of energy metabolism and partially prevents blockage of some synthetic processes (synthesis of neurotrophins is partially preserved) [27,31].

No pharmacokinetics of Actovegin, Cortexin, Cerebrolysin has been properly examined. That's why it is not clear which components of the medicinal agents penetrate through the blood-brain barrier (BBB) and to what extent [32].

Neurometabolic agents with a marked mnestic activity. This group is not homogenous and contains as follows:

- GABA derivatives: aminalon (gammalone), picamilonum, pantogam (pantocalcin).
- Derivatives of pyridoxine: pyriditol (encephabol, enerbol, cerebol).
- Medicinal agents containing dimethylaminoethanol: meclofenoxate, acephen, deanol, centrophenoxine.

These agents have similar mechanisms of action: they accelerate penetration of glucose via the BBB and improve its uptake by cells in different brain sections, activate synthesis of ATP and creatine phosphates, increase neuronal survival in hypoxia and ischemia, and improve cerebral blood flow. This results in more intense plastic processes in neurons and improves the brain integrative and mnestic activity [33,34].

In CVD, they are indicated in case of disturbed cognitive functions in CCVD during the restorative period after stroke. Homopantothenic acid preparations have a sedative psychopharmacological action. They decrease the motor excitability producing a simultaneous activating effect on working capacity and mental activity; they also produce an anticonvulsant action [34]. Pyritinol has a marked tonic effect, whereas the agents containing dimethylaminoethanol can cause excitation [35].

Neurometabolic agents containing succinic and fumaric acids (preparations based on Krebs cycle intermediates). Medicinal agents based on succinic acid include reamberin (1.5% solution for infusions) and cytoflavin (contains succinic acid, inosine, nicotinamide and flavin mononucleotide). The neurometabolic effect of Mafusol and Confumin is largely associated with succinate exchange (15% solution of sodium fumarate for infusions) [25].

Fatty acid oxidation inhibitors. Direct (partial) fatty acid oxidation inhibitors include ranolazine, trimetazidine, mildronate, whereas indirect ones include carnitine [25].

Mildronate is an analogue of gamma- butyrobetaine, carnitine precursor: it reversibly limits the rate of carnitine biosynthesis from its precursor gamma- butyrobetaine [36,37]. Trimetazidine inhibits 3-ketoacyl coenzyme A thiolase, which is one of the key enzymes of fatty acid oxidation almost in every tissue, including myocardium and brain [25]. Carnitine is important in transfer of long-chain fatty acids via the internal membrane of mitochondria and plays a leading role in formation and regulation of azetyl-coenzyme A [25]. D, L-carnitine chloride, L-carnitine (Elcar) and acetyl-L-carnitine (Carnycetin) are used [38,39].

Natural components of the respiratory chain. Antihypoxic agents which represent natural components of mitochondrial respiratory chain and participate in electron transfer are of practical importance. They include cytochrome C and ubiquinone (ubinon). These agents fulfil a function of replacement therapy as in hypoxia mitochondria lose a part of their components due to structural disturbances. Idebenone can be considered as ubiquinone derivate. It is (5 times) smaller than Q10 coenzyme, less hydrophobic and has a greater antioxidant activity [40–42].

Artificial redox systems. Antihypoxic agents with electron-accepting properties that form artificial redox systems compensate for deficiency of a natural electron acceptor (oxygen) in hypoxia. They bypass the respiratory chain links overloaded with electrons and thus partially restore its function. Moreover, artificial electron acceptors can ensure oxidation of pyridine nucleotides (NADH) in cellular cytosol preventing inhibition of glycolysis and excessive lactate accumulation. Oliphen (hypoxen) which is a synthetic polyquinone has been implemented into medical practice. Oliphen bypasses transport of electrons in mitochondrial respiratory chain (from complexes I and II to complex III), as its redox potential has values close to those of cytochrome oxidase [25].

High-energy compounds

Preparations of creatine phosphate (neotone) are used. Unlike ATP, it can penetrate via cellular membranes well [25]. Speaking about neurometabolic agents, it should be noted that their principal point of application in medical practice is represented by acute hypoxic and ischemic conditions which are the subject of urgent neurology. Not all the groups of preparations are used in therapy of a chronic neurologic pathology. They are commonly used as a component of complex treatment only.

NOOTROPICS

Nootropics (comes from Greek 'noos' = mind and 'tropos' = changed) are medicinal agents that produce a specific influence on higher integrative functions of the brain. They improve memory, make the educational process easier, both in a healthy person, and in case of disturbances [17,18]. A nootropic action is directly associated with the effect produced on certain structures of the brain. However, higher integrative functions of the brain can be improved indirectly (as a rule, in their abnormal decrease). For instance, this can be done due to improved cerebral circulation and microcirculation or optimization of metabolic processes in a neuron.

In the second case, it would be correct to mention not a 'nootropic effect', but 'a neurocorrecting or psychoenergetizing action' of the drugs. Considering the conditions, a group of nootropics includes a few compounds, when an effect on cognitive functions is prevalent, but not additional or indirect. These are derivatives of pyrrolidine (piracetam, pramiracetam, phenylpiracetam) and regulatory neuropeptides (noopept, semax, selank).

The nootropic mechanism of action is complicated, diverse and not studied yet. There is a well-reasoned point of view, according to which nootropics penetrate through the BBB and undergo metabolism. This results in formation of compounds that have structures similar to endogenous agents that regulate the processes of intellectual footprint formation and integrative brain activity. However, effect of nootropics on synthesis and degradation of these compounds is not excluded [18,33, 43–45].

There are two generations of nootropics. Generation 1 nootropics include pyrrolidine derivatives (piracetam, pramiracetam, phenylpiracetam); they intensify initial data treatment and memory consolidation. Generation 2 nootropic agent is a synthetical analogue of Noopept (memory dipeptide) and analogue of Semax regulatory peptides. Unlike pyrrolidine derivatives, the analogue produces an effect on all 3 phases of memory trace formation (processing): initial data treatment, data consolidation and extraction.

Piracetam

Piracetam has been used in clinical practice for five decades. It entered the market in 1972 under the name of Nootropil and was intended for treatment of memory and balance disturbances. Later appeared other piracetam-like compounds primarily used to treat cognitive disturbances such as pramiracetam, phenylpiracetam, oxiracetam and aniracetam (the last two medicinal agents are not used any longer) [18,44].

A positive clinical effect of piracetam is the most pronounced in patients with mild age-related cognitive disturbances and during the restorative period of ischemic stroke. In CVD, piracetam has a number of limitations: it is not used during the acute period of cerebral damage as it intensifies energy deficiency with anaerobic energy transfer and lactate formation (with possible acidosis); requirement of a cell in oxygen is increased under hypoxia (steal syndrome). Piracetam is also contraindicated in hemorrhagic stroke [45].

Phenylpiracetam (N–carbamoyl–methyl-4-phenyl-2--pyrrolidone) was implemented in medical practice in 2003 as Phenotropil. It is significantly superior to similar doses of piracetam by a nootropic activity and produces additional psychostimulating and anxiolytic effects [18].

Pramiracetam is piracetam derivative, where the amide group was substituted by 2-aminoethyl dipropan. Its bioavailability is similar to that of piracetam. However,

it has a greater activity and, thus, is used in smaller doses. Pramirocetam effectiveness was more pronounced in younger patients than in the elderly [18,44].

Noopept (memory dipeptide analogue — N-Phenylacetyl-L-prolylglycine ethyl ester) belongs to II generation nootropics, exhibits a marked mnestic and antiamnestic activity in significantly lower doses and much earlier than piracetam [18].

NEUTROTROPHIC AGENTS (NEUROTROPHIN SYNTHESIS MODULATORS)

The group includes medicinal agents that produce a direct effect on the synthesis of cerebral neurotrophic factors. As a high level of neurotrophins produces a neuroprotective (primary and secondary) and neurometabolic effect, neurotrophic agents are neuroprotectors and neurometabolics with equal effectiveness.

Availability of additional mechanisms of effect on the nervous tissue expands their therapeutic capabilities.

It is expressly asserted by now that **analogues of regulatory peptides** produce a direct effect on neurotrophin synthesis. Regulatory peptides (RP) are represented by universal endogenous bioregulators of cellular functions in human beings and animals. Structurally, they belong to oligopeptides being a part of the complex system of specialized signalling molecules that transfer information between cells of an organism. Their principal function is to integrate the nervous, endocrine and immune systems into a single functional continuum [46–49]. The system of regulatory peptides participates in regulation of almost any physiological responses by supporting essential balance (homeostasis) of all its systems. The specific feature of the regulatory peptide system is represented by multifunctionality in the majority of them, i. e. every compound can produce an effect on several physiological functions. Over 10,000 of various RP are known by now [48].

In a cerebral tissue, RP make the level of neurotrophic factors normal. The factors inhibit different mechanisms of a pathological cascade, on the one hand, and promote a better restoration of lost functions, on the other hand. This improves the functional plasticity of the cerebral tissue (a number and quality of connectivity is increased) and enables better restoration of lost functions [46–48].

As far as the group of regulatory peptide analogues goes, Semax is used in neurology, and Selank is applied in psychoneurology. Semax is a synthetic peptide made on the basis of $ACTH_{4–7}$ (Met-Glu-His-Phe) fragment with a marked physiological activity towards the CNS in the lack of hormonal activity. Pro-Gly-Pro tripeptide with a neuroprotective activity was attached hereto to protect from hydrolysis by peptidases [46].

The therapeutic action of Semax in CVD is based on normalization of neurotrophic factors in the brain tissue: it stimulates gene expression of many neurotrophins (neurotrophins –3, –4, –5, nerve growth factor (NGF) and brain growth differentiation factor (BDNF), m-RNA synthesis of neurotrophins and their receptors, increases the level of neurotrophins in the brain tissue [50–53]. Being a regulator of the brain neurotrophin synthesis, Semax is already an equally effective neuroprotector (decreases the possibility of primary and delayed neuronal death) and a neurometabolic agent [54].

Apart from the mechanism of neuroprotective action, Semax reduces the level of glutamate excitotoxicity accelerating transport of glutamate and aspartate from the synaptic gap to the astroglia; it possesses antioxidative activity associated with the increased activity of superoxide dismutase and a direct membrane protective action implemented due to altered physicochemical properties of plasma membranes [46,48].

Semax has a marked nootropic action, the mechanism of which is associated with an increased level of neuronal-based CREB (cyclic AMP response element-binding protein) phosphorylation [55]. An important pharmacodynamic property of Semax is its ability to regulate the functional activity of basic neuromediatory systems of the brain: cholinergic, serotonergic and dopaminergic [46].

Owing to the effect produced on the synthesis of neurotrophins and own direct effects, Semax prevents the death of penumbral neurons, inhibits abnormal apoptosis, enables restoration of connectivity and functions of glial cells, promotes rapid formation and/or restoration of an intellectual footprint; and improves higher cortical functions (attention, coordination of movements, speech, thinking) [46,48,55]. Overall, mortality and disability of patients with CVD, and disease progression rate are decreased; recovery of patients is accelerated (or remission time is increased), their socialization is improved [56–60].

CONCLUSION

The considered groups of neurotropic agents are components of neuroprotective therapy in neurology, which can be defined as a timely adequate effect produced on all pathogenesis factors that inhibit neuronal homeostasis at the systemic and neuronal level. Neuroprotection can be effective only in simultaneous use of activities that preserve neuronal vitality [61]. In particular, this is about support of arterial pressure at the levels ensuring adequate cerebral perfusion and corrected homeostasis of intracranial liquids.

The cornerstone of neuroprotective therapy is activation of protection mechanisms of neurons, endothelial and glial cells from the damaging effect of hypoxia by neurotropic agents [11].

Early use of neuroprotectors in acute CVD enables to do as follows [19]: 1) increase the rate of transient ischemic attacks and minor strokes among acute ischemic cerebrovascular disturbances; 2) significantly decrease the size of cerebral infarction; 3) prolong a therapeutic window expanding the possibilities for reperfusion therapy (thrombolysis); 4) protect from additional reperfusion (hyperosmolar and oxidant) damage in ischemic stroke.

The majority of the considered agents are the most effective in primary neuroprotection. It is aimed to interrupt the sequence of reactions (primarily of glutamate calcium cascade) that damaged neurons. It was the most effective within the therapeutic window when the nervous tissue damage hadn't become irreversible yet [11].

Secondary neuroprotection interrupts delayed neuronal death such as blockade of proinflammatory cytokine biosynthesis, molecules of cellular adhesion, autoimmune aggression, decreased intensity of oxidative stress, apoptosis inhibition, upregulation of neurotrophic factors. Nootropic agents are primarily used to treat cognitive disturbances.

Neurotrophic agents are the most universal ones. Thus, Semax has a remarkable primary and secondary neuroprotective activity, it is a neuroprotector and neurometabolic agent with equal effectiveness, it also has a marked nootropic action. In some cases, polypotency of Semax effects enables to carry out monotherapy reducing the patient's drug load.

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ASPECTS OF INFORMING AND OBTAINING CONSENT WHILE CONDUCTING TRIALS IN PULMONOLOGY AND PSYCHIATRY

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While obtaining voluntary informed consent from patients with chronic obstructive pulmonary disease (COPD), bronchial asthma and patients presenting with psychiatric symptomology who participate in clinical trials, it is necessary to remember not only about the rights and ethical standards, but also about an extremely vulnerable position of the participants due to their disease specificity. Changes in the mental status of the patients and principal problems of every patient need to be considered. In this article, the aspects of obtaining informed consent from patients with respiratory diseases such as bronchial asthma and COPD and those under psychiatric supervision are reviewed. Apart from general recommendations, every category of patients has its own specific features. Being aware of them will improve doctor-patient communication.

Key words: clinical trial, informed consent, vulnerable groups, bronchial asthma, chronic obstructive pulmonary disease, schizophrenia, depression

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АСПЕКТЫ ИНФОРМИРОВАНИЯ И ПОЛУЧЕНИЯ СОГЛАСИЯ ПРИ ПРОВЕДЕНИИ ИССЛЕДОВАНИЙ В ПУЛЬМОНОЛОГИИ И ПСИХИАТРИИ

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В клинических исследованиях, проводимых в группах пациентов с хронической обструктивной болезнью легких (ХОБЛ), бронхиальной астмой, а также у пациентов психиатрического профиля при получении добровольного информированного согласия необходимо помнить не только о правах и этических нормах, но и о том, что в данной процедуре принимают участие люди, находящиеся в крайне уязвимом состоянии в связи со спецификой каждого из заболеваний. В процессе получения информированного согласия у таких пациентов необходимо учитывать характерные для них изменения психологического статуса и принимать во внимание приоритетные проблемы каждого пациента. В этой статье рассмотрены аспекты получения информированного согласия у пациентов с заболеваниями респираторного тракта на примере бронхиальной астмы и ХОБЛ и у пациентов, находящихся под наблюдением врача психиатра. Каждая из категорий пациентов помимо общих рекомендаций имеет свои особенности, знания которых помогут в улучшении коммуникации между врачом-исследователем и пациентом.

Ключевые слова: клиническое исследование, информированное согласие, уязвимые группы, бронхиальная астма, хроническая обструктивная болезнь легких, шизофрения, депрессия

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Voluntary informed consent (VIC) is an important element of the system that guarantees compliance of medical experiments with ethical guidelines and observance of participants' rights. Every participant of a clinical trial (CT) should willfully and voluntarily provide the VIC [1, 2]. This can be a patient or healthy volunteer who receives a medicinal agent during the trial or stays in the control group [2–4].

In accordance with International Harmonized Rules of Clinical Trials (ICHGCP), obtaining a VIC is a process that allows patients to confirm their consent to participate in the clinical trial after acquisition of exhaustive data about all aspects of the trial. Consent is expressed by signing the VIC form which the patient has already read [5].

Those joining a clinical trial go through an obligatory process of giving VIC. It is a key component of any biomedical research which allows to observe participants' rights and ethical standards. When getting and documenting the VIC, a researcher should follow regulatory requirements, rules and ethical principles mentioned in the World Medical Association (WMA) Declaration of Helsinki.

Getting consent is rather burdensome and time-consuming both for researchers, and for participants [3]. Patients should be included in clinical trials only when they obtained information about participants' rights, examined scientific issue, research methodology, medicinal agent, course of treatment, potential risk and benefit, possible alternative treatment and potential shortcomings associated with research procedures [4]. The researchers should always do their best to record the process and obtain the VIC in writing.

While working with a patient, it is necessary to remember that the person is vulnerable due to the existing disease. In its turn, the perception of illness influences the internal disease pattern which is subjective for every patient and diagnosis.

VULNERABLE PARTICIPANTS OR PATIENTS

Vulnerable participants include persons or groups of persons who can't give spontaneous consent to or refuse from participation in the trial, and persons who are willing to participate in the trial because they are expecting certain advantages [1, 2]. The participants include people with severe and incurable diseases, subjects from rest homes, patients with medical emergencies, minors, those placed with foster parents and guardians, and people who are not capable of conscious consenting to clinical trials. Vulnerable patients also include those with mental disorders or those who can provide their consent under pressure; beggars and unemployed people, people belonging to national minorities, homeless persons, migrants and refugees; people who can probably wish to enter clinical trials due to high expectations [1, 2, 6].

SPECIFIC NATURE OF OBTAINING INFORMED CONSENT FROM PATIENTS WITH BRONCHIAL ASTHMA AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Patients with respiratory diseases are included into a separate vulnerable group.

The act of breathing is a vital process for a human life, as without this, it only takes several minutes for death to occur. Patients with bronchial asthma (BA) and chronic obstructive pulmonary disease (COPD) belong to a separate group. Their participation in clinical trials and procedure of getting informed consent have some specific features.

It is known that a chronic respiratory disease influences the mental status of a subject. First of all, this concerns patients with BA and COPD [6–8].

COPD imposes a burden represented by dyspnea to a different extent, but on a constant basis. The burden produces an effect on patient's physical and social activity which is most commonly decreased. Bad perception of the future and the feeling of hopelessness are developed. As a respiratory disease is progressing, dyspnea can even be more destructive, incapacitating and threatening, resulting in severe depression and anxiety [4]. In its turn, fear and anxiety can exacerbate dyspnea, result in hyperventilation symptoms and panic attacks, catching patients in a vicious circle and causing distress [7, 12].

During clinical trials, collaboration of doctors and patients, their involvement and readiness to participate, provision of feedback about the obtained treatment, therapy effect, occurrence of side symptoms and adverse events, and any changes observed in patients are important. The basis for successful conduction of a CT is formed when informed consent is obtained.

According to observations, patients know little about and are poorly informed of their disease [9]. During COPD aggravation, patients are commonly passive and wait for their symptoms to be relieved [10]. Under these circumstances, a medical investigator also has to increase patient awareness of the mechanism of pathological processes and existing possibilities to control the disease in order to improve the patient's personal responsibility.

A CT starts with obtaining informed consent. Proper communication with a patient is important. Good doctor-patient relationship means better adherence to treatment [11]. It has been shown in the MIRROR trial that patients with COPD are usually dishonest with their treating physician and medical personnel, whereas doctors may be not aware of the fact and underestimate it. Moreover, doctors and patients treat different symptoms in a different way. Thus, doctors pay more attention to dyspnea, whereas fatigue and pulmonary rales seem more important to patients [7]. It is necessary to remember that the patients have depression and increased anxiety.

In the majority of clinical trials, an informed consent form is a long document with a vast number of specific terms that can seem terrifying to a patient. When building a correct dialogue with a patient, it must be remembered that explaining the essence of a CT, basic principles and treatment process is an important and necessary link in communication with a patient.

It is obligatory that a patient should be informed of potentially related trial design, frequency of visits, and temporary and transport inconveniences. Patients should be aware that their time, occupation and things to do are just as important and prioritized as the clinical trial.

Duration of conversation is important while obtaining VIC from a patient with COPD. Patients tend to concentrate on the reasons for their disease and display surprise because they have the disease. The study doctor needs to be patient and show empathy.

Though in real life COPD and BA are referred to by one word 'asthma' and the two respiratory diseases are sometimes confused, patients significantly differ not only by mechanisms of abnormal process development, but also by psychological characteristics. As a consequence, a study doctor needs to remember about the specific traits when talking to the patient.

In a series of trials, strong and serial communications were discovered between asthma and anxiety disorders, in particular, panic disorders, panic attacks, generalized anxiety disorders, phobia, etc. [13]. Thus, according to Feldman, up to 45.0% of patients with asthma have different psychiatric diagnoses [14]; 63.0% of patients with asthma who requested urgent assistance due to acute exacerbation of an underlying disease demonstrated signs of anxiety disorder [15]. This is probably associated with a disturbing nature of asthma symptoms and their unexpectedness.

While obtaining VIC in patients with BA, it's necessary to find out which therapy — especially urgent therapy — can be used, and pay their attention to a lack of limitations while requesting medical aid during a clinical trial. A patient must be sure that he/she can obtain any kind of medical aid as soon as asthma symptoms are developed. A study doctor needs to establish a dialogue with the patient and necessarily inform the patient that feedback with a doctor is provided.

The peculiarity of obtaining informed consent within a clinical trial in patients with respiratory diseases consists in unwillingness to read a long and multipage document. A study doctor needs to read it together with the patient, pay his/her attention to all peculiarities of a certain trial, patiently explain all specific terms and complicated moments.

We should bear in mind that the majority of potential volunteers who visited the clinic have already taken a decision to participate in the clinical trial before informed consent was obtained [16]. In

practical terms, it means that the process of signing an informed consent form starts before possible participants get their hands on the consent. Prior information of volunteers is essentially the first step to obtaining informed consent [17].

Researches of new biological molecules cover most of recent clinical trials in respiratory diseases. The agents, and such terms as 'biological therapy', 'targeted therapy', 'monoclonal antibodies' are all new. This is the part where many questions related to obtaining informed consent arise. All complicated and intimidating terms need to be 'translated' into a simple and non-medical language. Patients are interested how the agents influence the immunity and, especially, 'decreased immunity'. Biological molecules used in respiratory medicine are targeted at principle inflammatory mediators produced in disease pathogenesis and suppress their action. When the mechanism of action is explained to the patients, they try to understand whether and how exactly the general immune response is changed; which possible risks occur during suppression of a molecule. In this respect, the term 'a monoclonal antibody' sometimes becomes intimidating. For a study doctor, the term is just about the way of obtaining a molecule, and the doctor doesn't pay attention to it. However, the patient hears a new term and can interpret it in his/her own way (is it about cloning?). So, an explanation is obligatory. During the explanation, we need to look at the patient's reaction to every scientific term and explain what it means with an accessible language.

The effect produced by biological therapy on genome and reproductivity is another question that needs to be discussed when informed consent is obtained. It is necessary to give examples of already available biological molecules and describe the experience of their safe use by pregnant and nursing women, if any, and by pediatric population. Examples of successful and long-term use of biological agents in other areas of medicine (rheumatology and oncology) can be useful.

Many patients with COPD and BA, especially those with a severe course, develop signs of encephalopathies, which are progressing as the disease becomes more severe [18]. It has been shown in the majority of trials that patients with COPD have significant cognitive disturbances in general or in such areas as cognition, memory and motor functions [19]. Chronic hypoxemia typical of severe respiratory diseases is one of the most important key mechanisms that can produce a negative effect on neuropsychological and cognitive indicators [20, 21]. While obtaining informed consent from these patients, it is sometimes necessary to repeat information several times and/or use different wording.

SPECIFIC NATURE OF OBTAINING INFORMED CONSENT FROM PSYCHIATRIC PATIENTS

Psychiatric patients belong to another group of patients who require special attention while consent is obtained. Disturbance of various functions resulting from mental disturbances raise a great number of questions about the possibility of taking informed consent from psychiatric patients. It should be noted that the legal term 'lack of legal capacity' doesn't always correlate with the term 'incapability' as far as the ability to take decisions goes. Thus, patients who are legally competent can become incapable during certain periods of time as far as assessment of risks and advantages and taking informed consent are concerned. The principal complexity for a study doctor is to understand correctly whether a patient is capable to take an informed decision or not.

Comparatively small amounts of data that can be taken as a reference value have been accumulated to this date. That's why researchers have to take decisions based on their personal experience.

The conducted trials have shown that patients with schizophrenia have a more disturbed ability to take decisions as compared with patients who have depression and general population [21, 22]. However, patients with schizophrenia include those who can take decisions just similar to people without mental disturbances. According to the research results published in 2000 [23], when the ability of patients with schizophrenia, schizoaffective disorders and healthy volunteers to take decisions was compared, patients with schizophrenia are less capable of taking decisions but with a larger spread of data present. Similar results were replicated multiple times [24–26].

Though many efforts were spent on searching psychopathological correlates of decision taking ability, it has been shown that the strongest predictor of this ability is represented by neuropsychological functioning [27–29]. There is a definite correlation between cognitive manifestations of positive and negative symptoms of schizophrenia. Nevertheless, a patient's level of functioning mainly influences the awareness of a decision. Thus, a psychotic patient can provide informed consent.

But how can we determine whether a patient can consent to participation in a trial? International practice has several instruments at its disposal, which make it possible for a patient to provide informed consent. MacCATCR semi-structured interview (MacArthur Competence Assessment Tool for Clinical Research) is one of them. It takes 15–20 minutes to conduct an interview and estimate the patient's ability to take decisions.

Moreover, there exist several short versions of similar interviews: Brief Assessment for Consentto Clinical Research (BACO) [30] and Evaluation to Sign Consent (ESC) [31]. Nevertheless, the questionnaires are not translated and validated in Russian.

Using the questionnaires, we can find a group of risk with a reduced ability to take decisions. And then we face a dilemma of what can be done with these patients. Non-inclusion of them into a trial violates their rights due to the lost potential profit.

As it was written previously, researchers had to use their own experience and opinion when dealing with this issue.

The researchers who participated in the CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) big project have solved the problem with the help of the so called 'test subject's assistant' [32]. The person controls a patient's ability to provide informed consent to participate in the project. Apart from assessment of this ability during inclusion into the trial, the assistant exerts control over the patient during the entire project and can initiate its exclusion from the trial when the status is changed. This important fact takes into account a chronic nature of mental disturbances and therapy duration, whereas many trials are conducted separately. That's why the patient's ability to take a decision can be changed significantly.

Some authors say that various educational interventions within a week considerably increase awareness of patients with mental disorders [23–34]. Different thematic presentations and/or computer programs were used during similar trials as educational activities.

Just like in any other area of medical research, non-inclusion deprives patients of potential benefit. When a patient is unaware of a possible risk, researchers are facing a huge ethical challenge.

Nowadays there is no single solution to the problem. However, the issue can be highlighted due to special attention given by a researcher to patients from a high-risk group, conduction of various educational activities which seem clear to the patient, and attraction of third parties who allow to perform independent external control.

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OXYETHYLAMMONIUM METHYLPHENOXYACETATE, IMMUNOMODULATOR AND ADAPTOGEN: CLINICAL USE REVIEW

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Oxyethylammonium methylphenoxyacetate is an adaptogenic immunomodulator with a complex mechanism of action. It can be successfully used for treatment, prevention and restoration in case of flu and cold, and to improve working capacity in asthenia, including conditions developed following COVID-19. Clinical investigation of the effect produced by oxyethylammonium methylphenoxyacetate demonstrates its effectiveness under extreme climate and geographic conditions, during physical and mental overload, exercise, viral infections, severe infectious pathology, and all diseases associated with a weakened immune system. Based on conducted clinical trials of oxyethylammonium methylphenoxyacetate, no adverse effects were found and good tolerability was observed. Due to good compatibility of oxyethylammonium methylphenoxyacetate with other agents, it can be included into complex rehabilitation programs as an independent or/and complementary agent. This increases effectiveness of the conducted treatment and improves the diagnosis.

Keywords: oxyethylammonium methylphenoxyacetate, immunomodulator, adaptogen, efficacy, safety

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ИММУНОМОДУЛЯТОР И АДАПТОГЕН ОКСИЭТИЛАММОНИЯ МЕТИЛФЕНОКСИАЦЕТАТ: ОБЗОР ПРИМЕНЕНИЯ В КЛИНИЧЕСКОЙ ПРАКТИКЕ

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Оксиэтиламмония метилфеноксиацетат — адаптогенный иммуномодулятор комплексного действия, который можно с успехом использовать для лечения, профилактики и восстановления при простуде и гриппе, для повышения и поддержки работоспособности при астенических состояниях, в том числе после COVID-19. Клиническое изучение действия оксиэтиламмония метилфеноксиацетата свидетельствует о его эффективности в экстремальных климатогеографических условиях, при перегрузках в физическом и умственном труде, спорте, вирусных простудных заболеваниях, тяжелой инфекционной патологии, при всех заболеваниях, связанных с понижением иммунитета. На основании проведенных клинических исследований применения оксиэтиламмония метилфеноксиацетата не было выявлено побочных эффектов, отмечалась хорошая переносимость препарата. Благодаря хорошей совместимости оксиэтиламмония метилфеноксиацетата с другими препаратами он может быть включен в комплексные реабилитационные программы в качестве самостоятельного или/и дополняющего средства, что позволит повысить эффективность проводимого лечения и улучшить прогноз.

Ключевые слова: оксиэтиламмония метилфеноксиацетат, иммуномодулятор, адаптоген, эффективность, безопасность

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A principal problem that arises during the use of adaptogens is a lack of proven effectiveness, i. e., effectiveness in the trials conducted following strict rules. Effectiveness of adaptogens is most commonly a consequence of small trials (which, unfortunately, are not always correctly conducted) or experience of using traditional medicine which can sometimes be rejected with the help of evidence-based medicine.

It should be taken into account that from a chemical point of view, an adaptogenic agent is a complex combination of different substances which is difficult to analyze and reproduce. That's why the effect can vary lot-to-lot and is not always predictable.

A lack of proven effects observed during the use of adaptogens doesn't mean a complete lack of effects. Thus, some plant-based agents can influence metabolism of other medicinal agents and increase the risk of adverse effects. Wide use of plant-based agents in the absence of convincing evidence is related to ethical issues. Thus, further trials are required to obtain convincing evidence of adaptogen effectiveness and safety in clinical practice.

In recent years, oxyethylammonium methylphenoxyacetate, a biostimulator with immunomodulating and good adaptogenic properties, has been used in practical medicine. Its spectrum of action is similar to that of natural adaptogens (magnolia vine, ginseng, golden root, Eleuterococus, etc.). Nevertheless, in case with oxyethylammonium methylphenoxyacetate, these properties are pronounced to a significant extent [1].

Oxyethylammonium methylphenoxyacetate promotes interferon production, improves and corrects the immune status due to activation of cellular and humoral immunity links, promotes the phagocytic activity of macrophages, improves physical and mental endurance, decreases exposure to various toxins, enhances tolerance to hypoxia, low and high temperatures and other unfavorable environmental factors; has a marked antitoxic activity during intoxication with ethanol, organic solvents, and salts of heavy metals.

Oxyethylammonium methylphenoxyacetate produces immune- and hemostimulating effects, increasing tolerance to intensive physical and mental activities, hypoxia, overheating, overcooling, immobilization and pain stress, being an

adaptogen with a broad spectrum of action, and having marked antioxidative, antitoxic and membrane-stabilizing actions, anti-inflammatory, gonadotropic and anti-blast properties [2, 3].

Oxyethylammonium methylphenoxyacetate is approved for use in medicine as a broad spectrum adaptogen and in agriculture as a regulator of productivity and adaptive properties of plants, and also to improve reproducibility and productivity of animals, birds and beneficial insects [4–7].

The agent with low toxicity has antioxidative, reparative, anti-inflammatory, antitoxic, and energy-stabilizing (antiasthenic) effects [8–11].

According to the conducted trials, oxyethylammonium methylphenoxyacetate has demonstrated its effectiveness in combined therapy of out-patients (with cold, ARVI, flu, etc.) and in patients with severe somatic pathologies, including tuberculosis [7, 8].

Taking into account good compatibility of oxyethylammonium methylphenoxyacetate with other medicinal agents (MA), it can be included into rehabilitation programs as an independent or/and supplementary agent, increasing effectiveness of the conducted treatment and improving the prognosis.

Effectiveness of oxyethylammonium methylphenoxyacetate was shown during a complex therapy of patients with tuberculosis [12]. In the course of treatment of 30 patients with infiltrative pulmonary tuberculosis (17 men and 13 women who were administered 200 mg oxyethylammonium methylphenoxyacetate 3 times a day for 35 days) it has been found out that 13 men and 11 women had scarring and significant resorption of pulmonary tissue infiltrates; they had improved well-being and appetites, normal temperature and increased weight. In the control group, similar effects were found only in 3 men and 2 women during the same period of treatment.

The effect of 0.2 g of oxyethylammonium methylphenoxyacetate 3 times a day for 20 days was examined in a complex therapy of 37 patients with tuberculosis. Meanwhile, 19 patients with pulmonary tuberculosis had significantly accelerated absorption of infiltrates and earlier scarring of the pulmonary tissue during an X-ray examination. Improved hepatic function, increased appetites, higher body mass and normalized temperature were observed. 18 patients with extrapulmonary tuberculosis had improved health, better general tone, absence of weakness, more severe fatigue, and improved body mass. In all the cases, no worsened condition of the patients was observed, demonstrating effectiveness of oxyethylammonium methylphenoxyacetate for treatment of patients with tuberculosis [12].

During the next series of observations of 31 patients with fibrous and cavernous tuberculosis (17 men and 14 women who were administered 200 mg of oxyethylammonium methylphenoxyacetate 3 times a day for 90 days) it has been established that 10 men and 7 women had significant cavern scarring and less fibrosis, better well-being, less amount of produced sputum, better appetites, normal temperature and increased body mass. During the same period of treatment, similar effects were observed among 5 men and 4 women in the control group [7, 8].

In the complex treatment of 33 patients with posttuberculosis pyelonephritis (14 men and 19 women who were administered oxyethylammonium methylphenoxyacetate for 25 days) it has been shown that 8 men and 9 women had lower body temperatures with less pronounced or even vanishing clinical and laboratory signs of pyelonephritis. In the control group (30 patients), only 4 men and 1 woman had similar effects during the same period of treatment.

Kuznetsov IA et al. [13] have shown that clinical examination of the action produced by oxyethylammonium methylphenoxyacetate demonstrates effectiveness of this agent under extreme climatic and geographic conditions, physical and mental overload, exercise, viral infections, severe infectious pathology, and in case of all diseases related to immune deficiency.

Oxyethylammonium methylphenoxyacetate is used to prevent oncological diseases, and correct the psychoemotional status of narcological patients. It doesn't cause any complications, is well combined with many other medicinal agents, has no contraindications and builds up no tolerance [1].

Use of 0.2 g of oxyethylammonium methylphenoxyacetate a day for 20 days normalizes T- and B-cell-mediated immunity, increases both physical and mental working capacity. The sportsmen who took 0.3 g of oxyethylammonium methylphenoxyacetate a day for three weeks of training that uses speed and force experienced improved working capacity [14].

22 patients with neurocirculatory dystonia who were administered 0.1 g of oxyethylammonium methylphenoxyacetate 3 times a day for 20 days as a complex therapy had decreased weakness and fatigue during physical and mental stress. Use of 0.1 g of oxyethylammonium methylphenoxyacetate 3 times a day for 20 days as a complex therapy given to 28 patients with neurotic disorders also improved their quality of life. 24 patients from a psychiatric hospital and clinic of neurosis had normalized emotional background, improved motor activity and decreased weakness and fatigue. Treatment effect was manifested already on day 3–5 and augmented by the end of week 2 of using 0.3 g/day of oxyethylammonium methylphenoxyacetate for 20 days in combination with tranquilizers. On the other hand, asthenic and astheno-depressive states appear during abstinence and remission in patients with alcohol addiction.

Use of 0.6 g/day of oxyethylammonium methylphenoxyacetate for 20 days in patients with alcohol addiction who underwent treatment at a narcological clinic demonstrated a positive effect in all cases: headache, feeling unrested, heaviness in the head and other psychogenic disorders were decreased [13, 15–17].

Positive results were obtained when 0.1 g of oxyethylammonium methylphenoxyacetate was administered twice a day for three weeks to treat viral hepatitis (n = 32, hepatitis A as established diagnosis). Clinical and laboratory observations have shown that 30 patients from the control group who were not administered oxyethylammonium methylphenoxyacetate developed hepatomegaly on day 10–14 and were discharged on day 20–21. Two of them had elevated transaminase levels. All patients with hepatitis A who were administered oxyethylammonium methylphenoxyacetate were discharged on day 17–18 with normal biochemical values. Bilirubin level reduced twice or thrice on day 5, liver volumes were normalized by day 7–10, no allergic and toxic reactions were found [7].

In the subsequent observations, clinical effectiveness of oxyethylammonium methylphenoxyacetate and its effect on parameters of the immune system were examined in 38 patients who had moderate acute virus hepatitis B with an anticipated chronic outcome. 100 mg of oxyethylammonium methylphenoxyacetate were given to patients 3 times a day for 21 days from day 15–16 of the disease.

Oxyethylammonium methylphenoxyacetate normalized biochemical parameters during early recovery, whereas in patients from the control group, the values became normal only three months after discharge and remained high even at 12 months after discharge in case of a chronic stage. Use of oxyethylammonium methylphenoxyacetate resulted in significantly increased levels of T-killers, decreased production of interleukin 1β, and reduced levels of circulating immune

complexes, DNA antibodies; 78.9% of patients had 50–300 pg/ml of serum interferon α. Treatment with oxyethylammonium methylphenoxyacetate resulted in DNA virus levels reduced 10 times and more. Within 12 months after discharge, 89.5% of patients who were administered oxyethylammonium methylphenoxyacetate had negative virus DNA testing results, and only 5.3% of patients had traces of virus DNA, whereas 5.3% (2 people) of patients with chronic hepatitis had rather high concentrations of it (the latter was observed in 12.4% of patients from the control group).

Moreover, effectiveness of oxyethylammonium methylphenoxyacetate was examined in 39 patients with viral hepatitis B and aggravated occupational history (long-term contact with toxic and chemical substances) and secondary immunodeficiency. Oxyethylammonium methylphenoxyacetate was administered in the presence of markers of viral replication (0.1 g twice a day for 2–3 weeks starting from the period of maximum viral replication against the background of generally accepted pathogenetic treatment). Within the course of treatment, the majority of patients (86.2%) significantly improved their condition manifested as reduced intoxication, decreased jaundice intensity and reduced liver volumes, and distinct management of the syndrome of cytolysis. Tolerance of oxyethylammonium methylphenoxyacetate was good, no adverse effects were found. 35 patients had no signs of immunodeficiency after treatment; significant reduction in serologic markers of HBV infection was noted following treatment and during the restoration period as compared to the control group.

Remote outcomes in patients with aggravated anamnesis who had viral hepatitis B and were not administered oxyethylammonium methylphenoxyacetate seemed less satisfactory (chronic hepatitis and bile duct damage were registered 4 and 2 times as frequently, respectively) as compared to patients who used agents for pathogenetic therapy in combination with oxyethylammonium methylphenoxyacetate [18].

Use of 0.6 g/day of oxyethylammonium methylphenoxyacetate for 20 days as a complex therapy in patients with infectious hepatitis resulted in an icteric period reduced for 5–6 days, more rapidly restored volumes of the liver, lack of nausea, vomiting, sensation of heaviness in the epigastrium and right subcostal area. Oxyethylammonium methylphenoxyacetate administered for 7 days decreased serum bilirubin levels in the majority of patients. The patients had normalized biochemical values 4–6 days earlier than those from the control group, the length of stay in hospitals was reduced on Day 3–4.

The obtained data show that the agent is effective in treatment of hepatitis A and B as an adaptogen and probably as an inducer of interferonogenesis. Oxyethylammonium methylphenoxyacetate reduces the need in other hepatoprotectors and immunomodulators [7].

Moreover, oxyethylammonium methylphenoxyacetate ensures effective treatment for herpes. Observations of 32 out-patients with herpetic fever and 22 out-patients with genital herpes have shown that 0.6 g/day of oxyethylammonium methylphenoxyacetate for 20 days combined with antiviral and symptomatic agents reduced objective signs of the disease 5–6 days earlier than in 40 patients in the control group. It means that oxyethylammonium methylphenoxyacetate can correct the immune status during the secondary herpetic infection, prolong the period of remission and improve the clinical picture [19].

Oxyethylammonium methylphenoxyacetate also produced a stimulating effect on the cardiac function of patients with acute myocardial infarction (AMI) and chronic heart failure (CHF), potentiated and prolonged the action of cardiac medications (Neoton, Preductal) [12, 20–22].

Use of 0.6 g/day of oxyethylammonium methylphenoxyacetate for 20 days in 44 patients with chronic heart failure during combination treatment reduced peripheral vascular resistance, improved ECG parameters and increased the quality of life of patients based on the results of conducted psychological tests. Similar results were obtained in patients with acute myocardial infarction [12, 13, 16, 17, 20, 23–27].

Patients with CHD (primary acute myocardial infarction) aged 30 to 75 have been under observation. Oxyethylammonium methylphenoxyacetate has been used in the background therapy. They started at 100 mg once a day before increasing the dose to 200 mg three times a day. The control group included those patients who had not taken oxyethylammonium methylphenoxyacetate. Examination of patients who were given 100 mg of oxyethylammonium methylphenoxyacetate 3 times a day for 20 days against the background of traditional therapy has shown a significant improvement of hemodynamic parameters already on Day 10 [7].

A dramatic decline in immunity was found in patients with purulent and necrotic wounds, especially during the postoperative period. This promoted effectiveness trials of oxyethylammonium methylphenoxyacetate in surgical practice. It has been found out that 37 patients operated on for pancreonecrosis who obtained 0.2 g of oxyethylammonium methylphenoxyacetate 3 times a day for 10 days during a combination therapy experienced better restoration with significantly reduced length of stay at the intensive care unit [13, 28–31].

In the article of Shabanov PD, Ganapolsky VP, et al. [4, 6] it has also been shown that oxyethylammonium methylphenoxyacetate normalizes the values of physical and mental working capacity and metabolic state during exposure to the cold. The medicinal agent has frigoprotective properties and can be recommended for use as a meteoadaptogen for stimulation, preservation and restoration of working capacity during exposure to the cold (in cold climate). It effectively corrected cardiovascular changes induced by cold stress, including Ruffier test results. The working capacity of those tested was ultimately improved. Endurance of the muscular system (dynamic dynamometry results) and PWC170 statoergometric test results (indirect values of physical working capacity) were improved while taking oxyethylammonium methylphenoxyacetate. Coordination of movements (fine motor skills), values of static and dynamic dynamometry, were preserved at the level of thermal comfort.

No statistically significant changes in mental capacity were found with oxyethylammonium methylphenoxyacetate. While taking placebo, mean values of physiological parameters were significantly similar to those from the control group. During exposure to the cold, the metabolic status of test subjects had high prooxidant readiness expressed as increase in malondialdehyde levels by 99% and diene conjugates levels by 62%, decreased activity of superoxide dismutase by 55% and reduced glutathione levels by 47%. During exposure to the cold, volunteers had increased levels of lactate by 54% with decreased levels of pyruvic acid by 37% demonstrating a change in effectiveness of oxygen-dependent utilization of carbohydrate metabolites with activated anaerobic glycolysis.

In the group of volunteers who received placebo, the nature of metabolic changes was similar to one in the control group. Test subjects who received oxyethylammonium methylphenoxyacetate developed less pronounced metabolic changes during exposure to the cold as compared to those in the control and placebo groups. Thus, compared with the

control group, the level of malondialdehyde was higher by 48% only, whereas the level of conjugated dienes was higher by 29% ($p < 0,05$). Activity of creatine phosphokinase dropped by 29%. Activity of superoxide dismutase, levels of reduced glutathione, lactate and pyruvate weren't different from the values measured under thermal comfort conditions [4–6].

Thus, oxyethylammonium methylphenoxyacetate acts at the level of cells (tissues), and effectively corrects metabolic changes when it's cold. The action is universal as it prevents and mitigates the effect of environmental unfavorable factors on any organ [4–6].

In the work of Rasulov MM et al. [10] it was noted that oxyethylammonium methylphenoxyacetate enhances resistance to unfavorable climate and toxic effects in an integrated manner, increases resistance to cold-related infections during prevention and treatment of patients with acute viral respiratory infections. Oxyethylammonium methylphenoxyacetate reduces protein degradation and generation, accelerates its synthesis, decreases toxic and drug load, risk of complications, corrects postinfectious asthenia, and prevents immunodeficiency after anti-infective therapy [2, 10, 32].

The purpose of another trial was to examine a possible use of oxyethylammonium methylphenoxyacetate within a complex program of physical rehabilitation of patients with arterial hypertension (AH) combined with abdominal obesity [33].

Use of oxyethylammonium methylphenoxyacetate in addition to background therapy with enalapril resulted in a significant decrease in the levels of triglyceride, low density lipoprotein cholesterol as compared to the control group, and a significant reduction in the end-diastolic volume, end-systolic volume, left ventricular myocardial mass and left ventricular myocardial mass index based on echocardiography data.

Use of oxyethylammonium methylphenoxyacetate in addition to background therapy of patients with AH and obesity significantly decreased the level of metabolic disturbances and produced a positive effect on cardiac hemodynamic parameters. Due to good tolerability with other agents, oxyethylammonium methylphenoxyacetate can be included in complex rehabilitation programs for patients with arterial hypertension and obesity as a complimentary agent improving exercise tolerance [33].

Thus, pursuant to evidence base, oxyethylammonium methylphenoxyacetate as a complex adaptogenic immunomodulator can be successfully used for treatment, prevention and restoration during cold and flu, to increase and support working capacity in asthenic conditions, including the ones after COVID-19. This is particularly relevant in the view of the epidemiological situation and can aid in adaptation to new climatic conditions [1].

Clinical investigation of the effect produced by oxyethylammonium methylphenoxyacetate demonstrates its effectiveness under extreme climate and geographic conditions, during physical and mental overload, exercise, severe infectious pathology, and all diseases associated with a weakened immune system. Oxyethylammonium methylphenoxyacetate is needed to prevent oncological disorders and correct psychoemotional status in narcological patients.

Oxyethylammonium methylphenoxyacetate increased resistance to acute respiratory diseases (ARD), activated immune processes, increased effectiveness of protein synthesis, normalized lipid exchange, somatometric and physiometric data. That's why oxyethylammonium methylphenoxyacetate can be recommended for broad application both in therapeutic, and preventive purposes [34].

Based on the conducted clinical trials of oxyethylammonium methylphenoxyacetate, no adverse effects were found, and good tolerability of the drug was observed. Oxyethylammonium methylphenoxyacetate leads to no complications, has no contraindications and causes no addiction [13]. Due to good compatibility of oxyethylammonium methylphenoxyacetate with other agents, it can be included into complex rehabilitation programs as an independent or/and complementary agent. This increases effectiveness of the conducted treatment and improves the diagnosis.

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3D BIOPRINTING: ISSUES OF BIOETHICS

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Scientific development of 3D bioprinting is rapidly advancing. Bioprinting is expected to be actively implemented within the healthcare industry producing a revolutionary impact on transplantation. However, the innovative biotechnology involves numerous ethical and regulatory issues. Special attention is given to ethical issues associated with the use of embryonic cells, storage of personal data, obtaining informed consent, and peculiarities of clinical trials. The issues of safety and quality are reviewed. Equal access to technologies and use of biotechnologies to 'enhance a human being' are addressed. The issues of culture and religion are separately discussed within the context of this technology. It is stressed that as far as the issue of ethical estimation and legal regulation goes, 3D bioprinting can't be completely assessed with the help of regular clinical trials or acting regulatory requirements. In particular, no suitable regulatory system or special documents regulating 3D bioprinting of tissues and organs and their subsequent transplantation are currently available in Russia or globally. Thus, it's necessary to develop requirements to safety, quality and effectiveness of technological processes and end products obtained with the help of 3D bioprinting with the best interests of generally acknowledged human rights.

Keywords: bioprinting, 3D bioprinting, bioethics, biotechnology, informed consent, tissue engineering, transplantation, regenerative medicine

Compliance with ethical standards: Khokhlov AL, Belousov DYu — writing a manuscript; Khokhlov AL — editing.

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ТЕХНОЛОГИЯ 3D-БИОПЕЧАТИ: ВОПРОСЫ БИОЭТИКИ

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Научные разработки 3D-биопечати стремительно развиваются. Ожидается, что биопечать активно внедрится в здравоохранение, произведя революцию в трансплантологии. Вместе с тем данная инновационная биотехнология включает множество этических и нормативных вопросов. Особое внимание уделено этическим проблемам, связанным с применением эмбриональных клеток, сохранением персональных данных, получением информированного согласия, особенностями клинических исследований. Уделено внимание вопросам безопасности, а также качества продукции. Затрагиваются аспекты равного доступа к технологиям, применения биотехнологии для «улучшения человека». Отдельно обсуждены в контексте данной технологии темы культуры и религии. Подчеркивается, что проблема этической оценки и правового регулирования заключается в том, что 3D-биопечать не может быть полностью оценена с помощью стандартных клинических исследований или действующих нормативных требований. В частности, в настоящее время как в России, так и во всем мире, нет ни подходящей нормативной базы, ни специальных нормативных документов, регулирующих трехмерную биопечать тканей и органов и их дальнейшую трансплантацию. В силу этого встает задача разработки требований к безопасности, качеству и эффективности технологических процессов и конечной продукции, получаемой с помощью 3D-биопечати, с максимальным учетом общепризнанных прав человека.

Ключевые слова: биопринтинг, биопечать, 3D-биопринтинг, биоэтика, биотехнология, информированное согласие, тканевая инженерия, трансплантация, регенеративная медицина

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From time to time there appear news about 3D printed organs. Researchers from around the world have only initiated working upon different technological solutions: from a group that printed a miniature kidney [1] and such technological solutions as BioAssemblyBot [2] to completely new methods that enable printing cardiac tissues for certain patients.

The bioprinting technology can help overcome limitations of modern methods in tissue engineering, including the long wait for transplants. In the nearest future, bioprinting can satisfy the needs both of the elderly and children with the bioprinting tissue or organ being capable of growing along with the patient.

However, the innovative biotechnology involves numerous ethical and regulatory issues. Just like any new technology, 3D bioprinting is associated both with capabilities and risks. Thus, simultaneous solution of various scientific and ethical issues is required. Some of them will be discussed in this article.

3D BIOPRINTING TECHNOLOGY

Traditional 3D printing means building three-dimensional solid objects from CAD-files (computer aided design files) by adding layer by layer. The most common type heats plastic or any other material and adds every layer of it onto a platform until an object is completely shaped.

Printed organs imply a slightly higher level of complexity. Three-dimensional (3D) bioprinting technology creates tissues and organs from aggregates of cells similar to a construction set. 3D bioprinters are specifically developed for this creation or bioprinting. They are used just like 3D printers for fitting

different figures together to compose a 3D model one layer at a time.

At the beginning of the 2000s, researchers have found out that living cells can be diffused through the nozzles of jet printers without any damage. However, having only cells is not enough, and culture medium is required. For this, gelatin microgel is currently used. It contains vitamins, proteins and other essential compounds.

Cartridges for printers are loaded with spheroids or cell suspension. Inside cellular spheroids, cells connect to each other through cell adhesion receptors (from Latin stem of *adhaesio*). Tissue spheroids are fused like two drops of oil in water driven by surface tension and due to cell reaggregation and migration. When fused, tissue-specific spheroids form tissue- and organ-specific structures with 'normal' morphology. Spheroids are incorporated into biomedical scaffolds (made of biodegradable polymers or collagen), yielding 3D structures, where they can turn into a completely functional tissue. One printed layer of cellular spheroids is covered with another one, and the layers are fused together. This is how a 3D living object (tissue or organ) is obtained [3].

Let's take a urinary bladder, a less complex organ, consisting just of two types of cells. First researchers scan the organ to determine its patient-specific shape and form. Then 3-dimensional scaffolds are created and patient's cells are added to the scaffolds. The thorough and hard work can last for up to eight weeks. Finally, a bioreactor system provides an optimal environment for cells to grow into the organ. When doctors transplant the organ, the scaffold has already disintegrated and will vanish following a surgery.

Ideally, all types of cells need to be included. For instance, while printing the kidney, nervous, granular cells, and cells of the lymphatic system can be excluded as basic renal functions (filtration and reabsorption) can be fulfilled without the cells [3].

Bioprinting of more complicated organs strongly depends on effective vascularization. Innervation of a printed organ or tissue is definitely desirable but not obligatory, at least during the first stages. Moreover, postimplantation reinnervation is possible in theory. Printed organs can't be preserved. Their vitality is supported due to a specific solution in the so-called perfusion bioreactor systems. The organ expires within several days prior to transplantation. After it has been transplanted, it is best used till the end of the patient's life [3].

Several companies specializing in bioprinting of tissues or implants but not organs already have some products ready for sale at their disposal. The products include Organovo [4], CELLINK [5], 3D Bioprinting Solutions [6], Particle3D [7], Aspect Biosystems [8], ROKIT Healthcare [9], Viscient Biosciences [10], Dimension Inx [11], and Poietis [12].

LEGAL FUNDAMENTALS

The Russian legislation lacks guidelines regulating creation and implantation of bioprinted human organs [13]. The current edition of Federal Law No. 180-FZ 'About biomedical cellular products' [14] can't regulate the use of human biological organs yet, as the Law doesn't consider the issues of organ transplantation. At the same time, Law of the Russian Federation No. 4180–1 'About transplantation of human organs and (or) tissues' [15] can't regulate the use of 3D bioprinted organs as they are artificial [13].

However, both 3D printers, and bioprinted organs and tissues obtained herewith, can be classified as medical devices, because the relations concerning their use are directly associated with health protection of citizens (art. 38 of Federal Law No. 323 'On fundamental healthcare principles in the Russian Federation', [16], GOST 31508–2012 Medical products. Classification in accordance with potential risk of using. General requirements [17]).

It should be noted that specialized software is also categorized as a medical device by the legislator. Thus, special permission must be obtained not only to conduct clinical trials, produce and implant bioprinted human organs, but also to create their templates (CAD-files) using special software.

Trials of 3D bioprinters and special software, clinical trials of bioprinted organs and tissues should be regulated by Order of the Ministry of Healthcare of the Russian Federation as of January 9, 2014 No. 2н 'On approval of the order of assessing compliance of medical devices in the form of technical trials, toxicological studies, clinical trials for state registration of medical devices' [18].

3D BIOPRINTING — NEW ETHICAL ASPECTS

Possible manufacture of living tissues for research and therapeutic purposes, including tissue restoration and replacement, results in previously unknown ethical issues without clearly established regulatory pathways. For instance, if all human organs can be artificially created and replaced, can the human being still be considered as a holder or an object of rights?

The type of used cells plays a key role in characterizing tissues with bioprinting. During transplantation of allogenic cells, we come across donorship-associated classical ethical issues:

- donor's confidentiality;
- donor's informed consent;
- ownership of donor cells.

Stem cells are commonly used as 'construction blocks' for bioproduction of human tissues and organs. The principal ethical issue of stem cells is represented by their 'source'. The use of human embryonic stem cells (ESC) was heavily criticized and has some limitations. The limitations are both of legal (like in Federal Law as of June 23, 2016 No. 180-FZ 'On biomedical cellular products' [14]) and ethical origin [19]. The principal cell source is represented by embryos or fetuses. That's why the issue of ESC obtaining is at the intersection of bioethical problems of determining the moral 'embryonal status', legal abortions and experiments involving human participants.

Another source of cells for bioprinting is represented by xenogeneic cells. In this case, social and religious aspects of using animal cells should be considered. Patients who underwent xenografting can have psychosocial personality-related problems. Moreover, it can happen that religious beliefs won't allow some patients to use cells taken from certain animals [20].

Emerging opportunities of differentiated cell reprogramming and creation of induced pluripotent stem cells (IPSC) eliminate ethical problems of using ESC or xenogeneic cells. IPSC can be persistently differentiated to any certain types of adult cells (from skin cells to cardiac muscle cells and neurons). Nevertheless, 3D printing of human organs using autologous IPSC is not neutral from an ethical point of view [21].

Cell reprogramming is far from being perfect as well. Our current principal issue is to develop methods of correct differentiation of all stem cells prior to transplantation. The risk of oncogenicity poses a serious problem while using IPSC [22]. To make IPSC-based therapy safe, genetic testing of stem cell lines for potential clinical application should be conducted [23]. However, this results in additional ethical and legal issues associated with collection, storage and use of personal genetic data [21].

DIGITALIZATION

Another aspect that should be considered in ethical assessment of bioprinting states that the technology is set by the digital model. 3D printing technology digitalizes material objects, eliminating the borders between the physical world and digital space. If 3D printing digitizes material objects, then bioprinting digitizes a human body. A person acquires dependence on digital embodiment of an own body or separate organs through the respective electronic 3D models [13]. Printed organs manufactured with biotechnologies on the basis of digital models will replace natural ones. It means that models will replace nature. Thus, a question is raised about the liability for development, estimation of 3D models (CAD-files), getting and use of legal rights.

PERSONAL DATA

Human digitalization makes the issues of confidentiality and privacy relevant, as digital 3D model of bioprinting will represent personal data. This requires special rules that regulate obtaining consent to storage, processing and use of the data in accordance with Federal Law No. 152-FZ 'On personal data' [24].

INFORMED CONSENT

The principle of voluntary informed consent is the fundamental principle of protection of human rights in biomedical research. During 3D bioprinting, problems can arise while obtaining informed consent in urgent situations, when the patient can't express his/her informed consent. Obtaining informed consent can be difficult when a participant can't take a decision about donorship (for instance, some patients can stay at intensive care units) [25].

CLINICAL TRIALS

Clinical trials are required to implement 3D bioprinting into routine clinical practice and eliminate associated risks [25]. As 3D bioprinting is developed within the paradigm of personalized medicine, every biotechnological product is manufactured on an individual basis and can require additional changes in the experimental design in every particular case. Thus, standard approaches to clinical trials such as double-blind randomized control trials can't be applied to 3D bioprinting [21]. Though biomaterials are personalized, procedure criteria and protocols can be standardized based on the first clinical trials [21].

Management of experimental trials of 3D bioprinting of human organs is a complex task as effectiveness and safety of custom-made organs can't be tested on other people. Thus, every person is the first test subject [21]. Issues about the risk-benefit ratio, inclusion criteria, for instance, participation of terminally ill patients in experiments, have been raised [21].

Unlike regular clinical trials with, for instance, possible slow dose adjustment, patients who participate in 3D bioprinting trials can have difficulties to exercise their right to withdraw from a trial following implantation of an artificial bioprinted organ. Interfering with 3D bioprinting can be limited as far as reversibility of the procedure goes (removal of a graft and all cells that grew out of it), and attempts of reimplantation can lead to subsequent damage of patients' health. Besides, a patient can lose a chance for alternative treatment due to participation in bioprinting research [25].

SAFETY

As 3D bioprinting is still a clinically unverified technology, any new treatment with 3D printers is risky. That's why patients must be well aware of health consequences.

The majority of trials were successful in the immediate future. Nevertheless, long-term trials *in vivo* are required to understand whether adverse events can arise. It is obvious that need in the source of cells for bioprinting raises ethical issues associated with embryonic stem cells in accordance with more widely spread ethical debates about their use. Just like in donorship of organs, cells must be similar at a genetic level. Otherwise, the future organ will be rejected by a body. Human stem cells must be used to manufacture an organ for a certain patient. To advance this technology, medicine should find a way to check and standardize manufacturing of the organ.

Moreover, there are risks of teratoma and cancer, graft displacement and migration, which are probably irreversible.

QUALITY

Key aspects of bioprinting management include liability for product quality. Consequently, quality control, service and working safety liability, and quality assurance issues can be essential.

EQUAL ACCESS TO TREATMENT

As 3D bioprinting will soon become a reality, it raises ethical issues concerning treatment of diseases in low-income earners.

Bioprinting is an expensive innovative solution which can probably contribute to the good of some members of a certain subgroup only. So, accessibility of this medical aid is highlighted.

3D bioprinting is another solution that doesn't change rules of game for everyone. It is not intended for the majority. In spite of the promise that organs will be printed at the request and provided to everyone in need, social disintegration of biological manufacturing is likely to arise, when only those who can pay for organs will benefit.

Multi-level system of therapeutic organ replacement is acceptable for those who can pay for a more durative life of own organs. They will probably have a significantly higher quality of life, as bioprinted organs help avoid negative effects of immunosuppressive drugs. At the same time, whereas some patients will wait for a donor organ to be transplanted, and take immunosuppressive agents for the rest of their lives to prevent graft rejection, those with low income will be content with worn-out organs taken from a living or deceased donor wherever they are available.

Bioprinting is focused on individual medical aid, but not on development of a universal treatment plan for all patients. Personalized medicine is costly; it widens the gap between the rich and the poor.

Ownership of printed bio-objects. Lawyers believe that bioprinting opens up a new territory which is different from the former legal regulation of medicine or traditional 3D printing as far as legal ideas of a body go. Thus, issues concerning belonging of implanted bioprinted organs, right and/or possibility to grow own organs are raised.

«HUMAN ENHANCEMENT»

Bioprinting can be used to improve human working capacity, force, speed and endurance. For instance, bioprinting allows

to produce stronger and more flexible structures that imitate natural human bones. 3D bioprinters can also improve working capacity of muscles.

«Human enhancement» will produce a dangerous, but unbelievable effect on the society; bioprinting can create a culture without diseases and imperfections. An ethical issue associated with possible printing of a unique human organ is raised, as this is related to a superhuman.

LEGISLATION

Bioprinting faces serious challenges on the part of technological, financial and regulatory practice. Bioprinted goods must be subject to state regulation.

As bioprinted organs don't correspond to the current rule of clinical trials, the existing rules need to be reconsidered and probably revised to guarantee safety of the products.

Moreover, bioprinting is a new topic to be examined and rules of biosafety in this area haven't been established yet. Adverse events in bioprinting were rarely taken into consideration, including such issues as degradation of biomaterials and tissue integration, biocompatibility and continuous tissue synthesis during material decomposition.

PROTECTION OF PERSONAL DATA

Exchange of data for research purposes increases a number of people who can get access to personal genomic data. In its turn, this improves the probability of data leakage and misuse, including for commission of an offence.

Management and conduct of human genome research and activity of the respective genetic companies are not regulated by the Russian legislation. Requirements to donor's consent to the research and requirements to processing and transfer of genetic data as a special category of personal data are not provided for in the acting legislation [26]. Moreover, the existing legislation provides for no turnover of biological materials withdrawn from donors for research, and neither protects donors' rights nor regulates obligatory preliminary consent of the research by ethics committees [27].

Bioprinting will have to select between limited and open use of the technology. An unregulated bioprinting market can lead to thriving black markets.

Moreover, there exist obstacles for commercialization and use of ESC-based 3D printing technologies. Thus, according to subpar. 3, par. 4, art. 1349 of the Civil Code of the Russian Federation 'the use of human embryos for industrial and commercial purposes… is excluded from patentability' [28].

CONCLUSIONS

1. 3D bioprinting is an extremely complicated technology with numerous social, legal and ethical problems. Researches and technological capabilities are developed much faster than our comprehension of ethical and legal consequences thereof. There is currently no system or specific documents regulating 3D bioprinting of tissues and organs and their subsequent transplantation neither in Russia, nor globally.
2. The problem of ethical assessment and legal regulation of 3D bioprinting is that the technology can't be completely estimated using standard clinical trials or acting regulatory requirements.
3. Rules of clinical trials need to be accepted to make 3D bioprinting more accessible. Informed consent to donation, manipulation with materials, their storage and subsequent use for commercial and research purposes is required.
4. Requirements to safety, quality and effectiveness of technological processes and end products obtained using 3D bioprinting must be developed taking into account human rights and dignity.
5. It is necessary to establish the rules of circulation and limits of commercialization of 3D bioprinting of human organs and tissues, and possible sanctions against illegal trade of artificial organs.

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