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Contents
Содержание

ELDERLY PATIENTS IN RANDOMIZED CLINICAL TRIALS: ETHICAL ISSUES

Butranova OI[1] ✉, Zyryanov SK[1,2]

[1] Peoples' Friendship University of Russia (RUDN University), Moscow, Russia

[2] Municipal Clinical Hospital No. 24 of Healthcare Department of Moscow, Moscow, Russia

Considering patients of elderly and senile age, pronounced discrimination continues to be observed, expressed in their insufficient inclusion or non-inclusion in randomized clinical trials. As a result, the clinical recommendations based on the results of such studies cannot be fully applicable to this category of patients. The problems of inclusion/non-inclusion of older people in clinical trials are numerous. The reasons for their occurrence and solutions affect, among other things, the ethical sphere. Compliance with basic ethical principles such as respect for persons, beneficence and justice should underlie the decision to include a patient in a study. In general, when evaluating these ethical principles from the point of view of the well-being of the entire population of elderly and senile patients, it is necessary to rethink the principles according to which this category of patients was excluded from clinical trials.

Keywords: elderly patients, randomized clinical trials, ethical principles

Author contribution: Butranova OI — literature analysis, collection, analysis and writing the text for publication, research planning; Zyryanov SK — data analysis and interpretation.

✉ **Correspondence should be addressed:** Olga I. Butranova
ul. Miklukho-Maclay, 6, Moscow, 117198, Russia; butranova-oi@rudn.ru

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ПОЖИЛЫЕ ПАЦИЕНТЫ В РАНДОМИЗИРОВАННЫХ КЛИНИЧЕСКИХ ИССЛЕДОВАНИЯХ: ЭТИЧЕСКИЕ АСПЕКТЫ

О. И. Бутранова[1] ✉, С. К. Зырянов[1,2]

[1] Российский университет дружбы народов (РУДН), Москва, Россия

[2] Городская клиническая больница № 24 Департамента здравоохранения города Москвы, Москва, Россия

В отношении пациентов пожилого и старческого возраста продолжает наблюдаться выраженная дискриминация, проявляющаяся в их недостаточном включении либо невключении в рандомизированные клинические исследования. Как следствие, формируемые на основании результатов подобных исследований клинические рекомендации не могут быть в полной мере применимы по отношению к рассматриваемой категории пациентов. Проблемы включения/невключения пожилых людей в клинические исследования многочисленны. Причины их возникновения и пути решения затрагивают в том числе этическую сферу. Соблюдение основных этических принципов, таких как уважение личности, благодеяние и справедливость, должно лежать в основе принятия решения о включении пациента в исследование. В целом, оценивая данные этические принципы с точки зрения благополучия всей популяции пациентов пожилого и старческого возраста, необходимо переосмыслять принципы, согласно которым данная категория пациентов исключалась из клинических исследований.

Ключевые слова: пожилые пациенты, рандомизированные клинические исследования, этические принципы

Вклад авторов: О. И. Бутранова — анализ литературы, сбор, анализ, написание текста публикации; С. К. Зырянов — анализ, интерпретация данных.

✉ **Для корреспонденции:** Ольга Игоревна Бутранова
ул. Миклухо-Маклая, д. 6, г. Москва, 117198, Россия; butranova-oi@rudn.ru

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The principles of evidence-based medicine underlie all modern clinical guidelines for managing patients, regardless of nosology, and their observance guarantees the best result in terms of outcomes. But is this true in the case of elderly and especially senile patients? The principles of the hierarchy of evidence put on the first-place systematic reviews and meta-analyses, as well as randomized clinical trials (RCTs). The proportion of elderly and senile patients in the total volume of RCTs is very small: for example, from January 1990 to December 2002, only 84 RCTs were found including patients over 80 years of age, of which 75 studied the effectiveness of therapy, and 9 — safety [1]. For comparison, over the same period, the total number of RCTs in young and adult patients was about 50,000. Most of the cardiovascular drugs, hypoglycemic drugs, and many others are used mainly by patients of older age groups. At the same time, according to Konrat C, et al (2012), in most RCTs estimating effects of drugs which are mainly used in the treatment of diseases specific to elderly patients, the proportion of participants over 65 was less than half. This pattern was typical for 62.2% RCTs of pioglitazone, 40.9% RCTs of risedronate, 37.9% RCTs of rosuvastatin, and 70.2% RCTs of valsartan [2]. An analysis of phase III clinical trials carried out by the National Institutes of Health, USA, from 1965 to 2015, found a significant disproportion between the studied nosologies and the participant profile, manifested in the inclusion of relatively young patients in studies on diseases typical of the elderly (chronic heart failure, osteoarthritis, etc.). In particular, it was demonstrated that in 67% of the studies the mean and/or median age was less than expected for the disease or condition of interest. Based on their analysis, the authors suggested that the results of these studies cannot be extrapolated to the general population of older people [3]. The COVID-19 pandemic has affected mainly the elderly and senile patients, while the age of patients included in RCTs studying

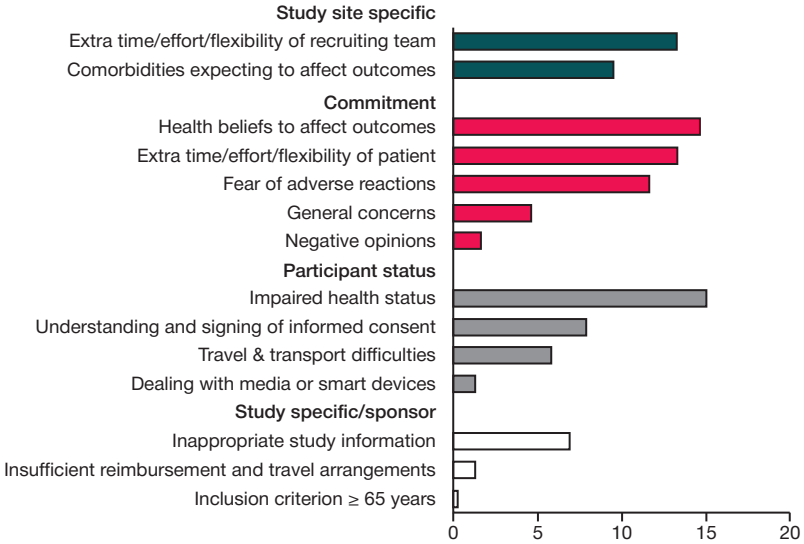

Fig. 1. Comparative assessment of the significance of problems associated with the inclusion of elderly patients in RCTs. Mean number of points awarded per item (standard error range: 0.17–9.17) (reproduced from [8]).

the efficacy and safety of drugs aimed at the treatment of COVID-19 was 20 years younger than the average age of patients included in observational studies [4]. If we consider RCTs of diseases that are common not only among the elderly, but also in other age groups, here the recruitment of participants is almost always limited to young patients. In the analysis of 32 RCTs of atopic dermatitis (n = 4547), the average age of participants was 34.4 (+5.4) years, while only 31% of the RCTs included patients older than 65 years [5]. In recent years, there has been some increase in the trend to include older patients in RCTs, but this affects only patients slightly older than 65 years, patients of the 75 plus age group still have a minimal representation in the structure of RCT participants. An analysis of RCTs published in one of the journals with a high impact factor between March 2019 and March 2021 found that only 8.3% of the studies had an average age of participants over 75 years [6].

In addition to the insufficient inclusion of older patients in RCTs, the problem is the qualitative characteristics of those older people who were nevertheless included in the studies. An analysis of data from UK phase III/IV trials (n = 116) of new drugs for the treatment of chronic diseases found that the proportion of older patients participating in studies with 2 or more comorbidities was in most cases about 30%, which is below the average values for population of elderly patients [7].

The global exclusion of elderly and senile patients from RCTs is in many ways unjustified and even dangerous, since in the future the results of RCTs are used as the basis for developing therapeutic strategies for this category of patients. A balanced assessment of the ethical principles for including or not including elderly and senile people in RCTs can serve as one of the tools aimed at improving the quality of care for elderly and senile patients.

ETHICAL ISSUES OF THE INCLUSION OF OLDER PATIENTS IN RCTS

The conclusion made by the multidisciplinary expert panel regarding the problems associated with the inclusion of older patients in RCTs stated that the key barrier to inclusion is poor health and a higher prevalence of acute or chronic comorbidities in this age group. In general, the experts identified four groups of recruitment problems: related to the study site, to the commitment, to patient/participant status and to the study/sponsor. Figure 1 represents the average scores assigned by experts to each of the problems (a 20-point scale was used), as well as the details of their compounds [8].

From the patient's point of view, the risk of health damage leads to reluctance to take the study drug, which may lead to violations of the regimen prescribed in the study protocol. As a result, the outcomes in such patients will distort the overall results, which corresponds to the point of view of the RCT organizers, who are negative about the prospect of including older patients.

The common opinion of many researchers is that the problems of including elderly patients in RCTs are associated with the patient's inability to understand the purpose of the study and its stages, the inability to follow the protocol, and, most importantly, the inability in many cases to give an informed consent (IC) to participate in the study. [9].

Modern provisions on the protection of the patient as participant of a clinical trial were set out in the Helsinki Declaration of 1964, which is advisory in nature. In the Russian Federation, the Rules of Good Clinical Practice of the Eurasian Economic Union are currently used as a regulatory document. Actually, the use of the imperative of consent to the implementation of medical or diagnostic procedures is an achievement of the 20th century and states like: "every person in adulthood and in his right mind has the right to determine what to do with his body" [10]. With regard to research practice, the "Berlin Codex" was the first normative document [11], and the doctrine of informed consent, close to the modern one, was formulated in the late 1940s. within the framework of the Nuremberg Code [12]. It is important to note the three basic ethical principles of research practice formulated in the Belmont Report [13]:

- respect for the individual;
- beneficence;
- justice.

The IC procedure demonstrates the principle of respect for the individual, while its signing, as well as the actual participation in the RCT of an elderly person, requires a detailed assessment by the doctor of all the pros and cons in relation to such principles as beneficence and justice. Assessment of the capacity of an elderly patient before signing an IC is an important step that can determine the success of participation

in the study as a whole. There are various tests aimed at assessing the main components of the mental capacity [14], including the degree of understanding (receiving and processing information), value of judgments (evaluating information in an individual context), reasoning ability (comparing alternatives and understanding the consequences) and the ability to make choices (determining one preferred option and a message about the choice).

The actual process of signing an IC can act as an additional stress factor for the patient, increasing the state of anxiety. There is discussion of the possibility of an alternative to a written signature for older patients, such as the use of a seal, thumbprint, head nodding and handshake [15]. Such alternatives may help to reduce stress in the elderly patient associated with the provision of a written signature [16], but the legitimacy of such alternatives is debatable. Disorders in the mental sphere represent a significant problem: the progression of dementia and cognitive decline act as a factor limiting the patient's ability to participate in the study. The signing of the IC by the legally authorized representative is a possible option, but, from an ethical point of view, quite controversial, since in this case the personal desire or unwillingness of the patient remains unknown.

Additional problems in conducting RCTs arise in the case of the participation of elderly and senile patients who are residents of nursing homes, suffering from dementia, or who are in the intensive care unit (ICU). The ability to perceive information and value judgments in such patients is significantly reduced, which leads to the inability to sign the IC. In this regard, data from an analysis of 269 RCTs involving elderly patients in the ICU setting are of interest. The results found that in 8 out of 269 RCTs, the protocol noted the refusal to use IC, in 5 — exemption from the procedure for signing IC, in other 9 information about the IC procedure was not indicated, but its presence was assumed [17]. Of the 256 RCTs with IC, 70.7% had written consent, 1.2% had both written and oral consent, 1.6% had only oral consent, and 26.5% did not specify the type of consent.

The signing of an IC by an elderly patient does not guarantee his participation in the study. The rate of non-participation among elderly after signing consent has been shown to be higher than in younger patients. In the work of Hempenius L et al (2013), refusal to participate in the study was noted in 16.8% of elderly patients, while problems with patient transportation and procedure planning caused only 3.7% of participants to be excluded from the study [18]. In this regard, an important stage is the explanatory work provided by the doctor, which necessarily includes building a trusting relationship with the patient and is aimed at reducing anxiety and negative expectations of the elderly person.

Another problem is premature discontinuation of the study, which is typical for the elderly and senile; according to published data, the proportion of such patients can reach 30% [19], which can lead to difficulties in the final analysis of the data.

RECOMMENDATIONS FOR ETHICAL INCLUSION OF ELDERLY PATIENTS IN RCTS

Age-related changes in organs and systems, senile asthenia, impaired cognitive functions, the presence of polymorbidity and, as a result, polypharmacy limit the possibility of including elderly and senile patients in RCTs. At the same time, these conditions are widespread in real clinical practice, and therefore the inclusion of such patients is highly desirable in terms of obtaining highly reliable results that could be directly implemented in real schemes for managing elderly and senile patients. Assessing the risks and problems of including older patients in RCTs, it can be noted that their non-inclusion, the introduction of strict age limits, the declaration of polymorbidity and senile asthenia as non-inclusion criteria lead to an obvious distortion of such fundamental ethical principles as beneficence and justice. This is especially true in relation to the further receipt of modern high-quality medical care by the general population of elderly and senile people.

The traditional approach to planning RCTs includes the introduction of age restrictions, it is believed that patients over 70–75 years of age will not be able to comply with the requirements of the protocol and have a high risk of premature discontinuation of the study. On the other hand, older patients may have more free time to participate in RCTs and, provided that cognitive functions are preserved, they may be sufficiently involved in the process of providing data about themselves and fulfilling the requirements corresponding to the stages of the study [20]. Evidence has been published showing the benefit of removing the upper age limit for enrolling patients in RCTs and reducing the list of exclusion criteria in terms of improving the quality of evidence obtained in RCTs [21].

Considering possible options for solving the problems associated with the inclusion / non-inclusion of older people

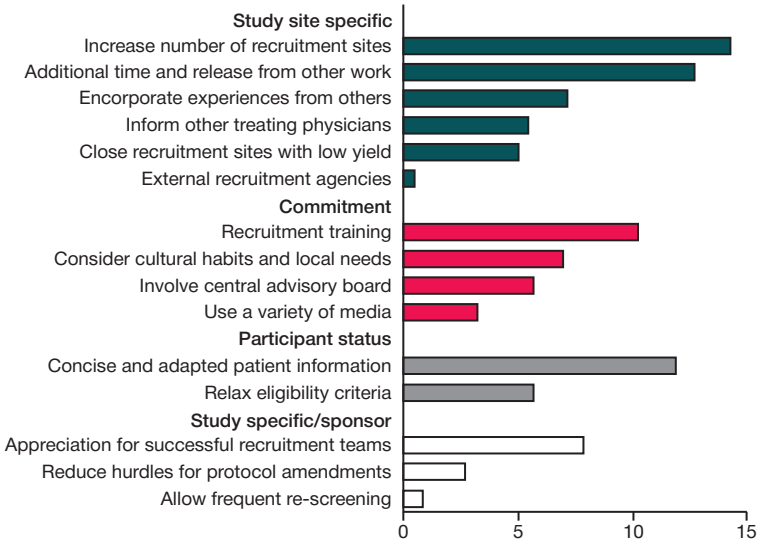

Fig. 2. Comparative assessment of the significance of options for solving problems associated with the inclusion of elderly patients in RCTs (in points) (from [8]).

in RCTs, it is worth noting the results of a survey of experts involved in conducting studies involving this category of patients. According to their collegiate opinion, the most important thing for a larger recruitment of older participants is the inclusion of more research centers, as well as the allocation of more time to staff with their release from other duties, staff motivation, expressed in financially expressed gratitude for the successful inclusion of patients. Great importance is attached to the reduction and simplification of information about the study provided to patients (Fig. 2). Taking into account the expert opinion presented, it can be noted that the problems are solvable, and the solution lies mainly in the area of increasing the funding of RCTs involving elderly patients (increasing the cost of including additional research centers, attracting additional staff).

Ethical issues of participation of elderly and senile patients in RCTs affect both the patients themselves and the researchers. The use of the "do no harm" principle should be fundamental at all stages, including screening, signing an IC, and actually participating in the study. The existing discrimination of older people in relation to inclusion in RCTs can be regarded as a violation of equal rights, however, the patient's misunderstanding of the objectives of the study and the conditions for participation may lead to a violation of such an ethical principle as a beneficence, expressed in the final impact of the study on health and quality of life indicators in elderly persons. The development and implementation of new medical technologies is aimed at providing high-quality and safe care to patients, this process is impossible without RCTs. The non-inclusion of elderly patients in RCTs is a fundamentally significant mistake leading to a global decrease in the effectiveness of the technologies used, which means that in relation to the population of elderly patients, we are faced with a violation of all three basic ethical principles simultaneously: respect for the individual, beneficence and justice.

CONCLUSION

The exclusion of patients from RCTs on the basis of age, depending on the degree of cognitive impairment and polymorbidity, hinders scientific progress in the treatment of elderly and senile patients. Rethinking existing approaches to the inclusion of this category of patients in RCTs is essential to improve the efficacy and safety of developed therapeutic strategies and improve treatment outcomes, as well as to protect both the study participants themselves and researchers.

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ETHICAL ISSUES IN GERIATRIC CARE

Butranova OI[1] ✉, Ushkalova EA[1], Zyryanov SK[1,2]

[1] Peoples' Friendship University of Russia (RUDN University), Moscow, Russia

[2] Municipal Clinical Hospital No. 24 of Healthcare Department of Moscow, Moscow, Russia

Increased life expectancy along with an increasing share of elderly and senile patients in the structure of the population make the tasks of longer healthy life expectancy pressing. A set of activities aimed at optimization of management of patients within the framework of gerontological practice should include elimination and prevention of diagnostic and therapeutic errors. The basic risk factors of medical errors include high heterogeneity of elderly and senile patients, overburdened healthcare system, polypharmacy, including due to parallel prescription of drugs to the same patient by multiple medical professionals, concomitant diseases, and high comorbidity, measured by the Charlson Comorbidity Index. Mismanagement of elderly patients can result both from underestimated severity of the patient's conditions, and from hyperdiagnostics. Typical errors of pharmacotherapy include use of potentially inappropriate medications, potential prescribing omissions, simultaneous prescription of drugs with high risk of clinically significant interactions, incorrect selection of dosage without taking into account the renal failure, which is associated with high risk of toxic effects. Affordability of medical aid for an elderly patient is another important social aspect influencing the patient's quality of life. As far as basic ethical principles of management of elderly and senile patients go, it is necessary to respect independence, well-being and justice for the patients regarding possible obtaining of qualitative medical aid as compared with other age groups.

Keywords: elderly and senile patients, medical errors, polypharmacy, accessibility of medical aid, ethical principles

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✉ **Correspondence should be addressed:** Olga I. Butranova
ul. Miklukho-Maklaya, 6, Moscow, 117198, Russia; butranova-oi@rudn.ru

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ПАЦИЕНТЫ ПОЖИЛОГО И СТАРЧЕСКОГО ВОЗРАСТА В КЛИНИЧЕСКОЙ ПРАКТИКЕ: ЭТИЧЕСКИЕ ПРОБЛЕМЫ

О. И. Бутранова[1] ✉, Е. А. Ушкалова[1], С. К. Зырянов[1,2]

[1] Российский университет дружбы народов (РУДН), Москва, Россия

[2] Городская клиническая больница № 24 Департамента здравоохранения города Москвы, Москва, Россия

Рост средней продолжительности жизни наряду с возрастанием доли пациентов пожилого и старческого возраста в структуре населения делают актуальными задачи по увеличению продолжительности здоровой жизни. Комплекс мероприятий, направленный на оптимизацию ведения пациентов в рамках геронтологической практики, должен включать устранение и профилактику диагностических и терапевтических ошибок. Основные факторы риска врачебных ошибок — высокая гетерогенность популяции пациентов пожилого и старческого возраста, перегруженность системы здравоохранения, полипрагмазия, в том числе вследствие параллельного назначения препаратов одному пациенту врачами различных специальностей, наличие сопутствующих заболеваний, высокие значения индекса коморбидности Чарлсона. Неверная тактика ведения пожилых пациентов может быть следствием как недооценки тяжести состояния пациента, так и гипердиагностики. Типичные ошибки фармакотерапии включают применение потенциально не рекомендованных ЛС (ПНЛС), потенциально упущенные назначения ЛС (ПУНЛС), одновременное назначение ЛС, вступающих в клинически значимые взаимодействия между собой, неправильный выбор дозы, часто без учета нарушения функции почек, что сопряжено с высоким риском возникновения токсических эффектов. Доступность медицинской помощи пожилому пациенту является еще одним важным социальным аспектом, влияющим на качество жизни пациентов. С позиций основных этических принципов ведения пациентов пожилого и старческого возраста можно отметить необходимость обеспечения уважения автономности пациентов, их благополучия и справедливости в плане возможности получения качественной медицинской помощи в сравнении с другими возрастными группами.

Ключевые слова: пациенты пожилого и старческого возраста, врачебные ошибки, полипрагмазия, доступность медицинской помощи, этические принципы

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✉ **Автор для корреспонденции:** Ольга Игоревна Бутранова
ул. Миклухо-Маклая, д. 6, г. Москва, 117198, Россия; butranova-oi@rudn.ru

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Global changes in the way of life, achievements of modern medicine, higher quality of medical aid and its accessibility resulted in an increased life expectancy and rise in the proportion of senile persons in the population. During the past century, life expectancy doubled almost twice [1]. In North American and European countries, including Russia, percentage of the elderly was increased owing to the trend towards lower fertility. As a result, the current demographic situation was characterized by the unprecedented ageing of the population. In 2019, every 11th person in the world was elder than 65 years. According to prognosis, the group will include every 6th person by 2050 [2]. In Europe, more than a quarter of population (190 bln.) have already reached the age of over 60 [3], whereas percentage of the Russians elder than 65 in 2021 amounted to 15.8% [4].

Unlike the total life duration, healthy life duration is growing at a much slower pace [5]. Death is preceded by even a longer period of morbidity and multimorbidity [6]. If the median of life expectancy constitutes 71.4 years globally and 76.8 years in Europe [7], the median of healthy life amounted to 63.1 and 68 years, respectively [8]. The observed demographic processes contribute to a significant growth of percentage of the elderly both within the primary link of rendering medical aid, and among hospitalized patients.

Elderly and senile patients differ from the younger ones by involutionary functional and morphological changes in various organs and systems, mainly by a chronic course of diseases, their atypical clinical signs, geriatric syndromes, comorbidity and social and mental misadaptation. In this respect, standard principles and recommendations related to diagnostics and treatment can be unacceptable for this category of patients. This is confirmed by numerous diagnostic and therapeutic problems found among the elderly and senile patients in real medical practice.

DIAGNOSTIC AND THERAPEUTIC ERRORS IN GERIATRICS

In countries with high economic income, medical errors are the third leading cause of death among patients of any age; in the USA, they annually lead to 250,000 of lethal outcomes (9.5% of all deaths) [9]. Meanwhile, many mistakes, including the ones leading to lethal outcomes, are observed among elderly and senile patients [10]. In a prospective observational trial with 803 patients (mean age of 48.34+9.4 years) it has been shown that the main risk factors of medical errors included age older than 60 years, overburden of the healthcare system (≥20 patients per one hour), ≥5 of administered medicines, presence of concomitant diseases, Charlson comorbidity index and administration of the same drugs by several doctors [11]. In accordance with other trials, every other doctor who prescribes a drug to a geriatric patient is associated with an increased risk of adverse reactions approximately by 30% [12].

Within the age group, diagnostic errors equally include both underestimated severity condition, and hyperdiagnostics; this results in improper selection of medical tactics and negative treatment outcomes [13]. Typical errors of pharmacotherapy include use of potentially inappropriate medications, potential prescribing omissions, simultaneous prescription of drugs with high risk of clinically significant interactions, incorrect selection of dosage without taking into account the renal failure, which is associated with high risk of toxic (and primarily nephrotoxic) effects. All these mistakes decrease effectiveness and/or safety of pharmacotherapy among elderly and senile patients [14].

Medical errors are mainly due to high heterogeneity of elderly population. They become higher in number as soon as their age is increased. Thus, the prevalence of potentially not recommended drugs varies from 30 to 61.9% [15–18] among the elderly and from 79.3% to 85.1% [19, 20] among those who are older than 80 years. The potentially missed prescriptions of drugs are found in more than a half of the elderly [21] and in 81.4% of senile patients [19]. According to some trials, potentially missed prescriptions of drugs are more commonly found among females. For instance, in a trial involving 440 women (mean age of 75,75±6,56 years), potentially missed prescriptions of drugs were found in 98.3% of cases [22].

An important factor leading to diagnostic and therapeutic errors includes disturbance of cognitive functions among elderly patients. In a systematic review of 80 trials, it has been established that the prevalence of cognitive disturbances among the elderly varies from 5.1% to 41% (median is 19.0%), whereas the incidence calculated based on analysis of 11 trials varies from 22 to 76.8 per 1,000 person years (53.97 per 1,000 person years in average) [23].

Influence of cognitive disorders on diagnostics was due to the fact that a patient with dementia can't estimate his/her condition objectively, forgets or fails to notice the symptoms, including the ones that reveal a potentially life-threatening clinical situation. It has been shown in the trials that patients even with moderate cognitive impairment (MCI) do not obtain the necessary aid that corresponds to the real severity of their condition. For instance, presence of MCI in patients who had myocardial infarction is associated with a lesser rate of catheterization of the heart (50% among patients with MCI vs 77% of patients without MCI; $p < 0.001$), coronary revascularization (29% vs 63%; $p < 0.001$) and cardiac rehabilitation (9% vs 22%; $p = 0.001$) [24].

Hypodiagnostics due to the presence of cognitive disturbances in a patient is referred to typical medical errors, especially the ones made by those who work at intensive care units. Interviews of physicians show that the priority is given to the assessment of the current status of the patient, physical and laboratory examination, whereas shortage of time, observed in case of severe condition of the patient, does not allow to use special questionnaires to determine the degree of disturbed cognitive functions [25]. A patient's cognitive sphere is more commonly assessed based on the data obtained from the relatives; diagnostic tests are applied more rarely; patients are sent to be consulted by specialists even more rarely [25]. The mentioned approaches lead to iatrogenic diagnostic and, as a consequence, therapeutic errors.

The degree of disturbed cognitive functions determines the borders within which the patient can show independence while taking decisions as far as treatment goes. The doctor has to determine the borders during the primary interview and examination. If the patient does not have the required active legal capacity, the doctor must decide who can or must sign an informed consent form instead of the patient. Another ethical problem, which results from assessment of the patient's independence, consists in the possibility of obtaining outpatient treatment, especially if the patient lives alone or with other legally incompetent family members.

It should be noted that staying with the persons who suffer from dementia leads to worsened health of their caregivers, especially when the care is provided by spouses of the same age [26]. In particular, spouses of patients with cognitive disturbances have an increased risk of depression, disturbed nutrition [27] and pain [28]. Thus, they should be reviewed as 'a priority group in healthcare' and obtain a complex social, economic and medical aid [28].

ACCESSIBILITY OF MEDICAL AID FOR AN ELDERLY PATIENT

An ethical aspect in the social dimension requires individual attention: can an elderly or senile patient get a proper access to medical aid? The issue is simultaneously related to several spheres: a patient's ability to reach a healthcare institution, readiness of a medical institution to give specialized aid and care to a patient with senile asthenia and cognitive disturbances, financial abilities of a patient to pay for diagnostics, treatment and rehabilitation. Research of accessibility of medical aid for elderly patients in Israel has shown that it was impossible to obtain medical aid for 20.5% to 40.9% of patients [29]. The reasons why patients of different age groups couldn't be consulted by a specialist are presented in table.

Table. Accessibility of medical aid for patients of different age groups (modified from [29])

Parameter	65–70 y. o.	76–89 y. o.	>90 y. o.	General population
Having difficulties in visiting specialists, n (%)	105 (20.5)	138 (29.5)	108 (40.9)	351 (28.2)
Economic difficulties in visiting specialists, n (%)	23 (22.8)	15 (11.2)	9 (8.4)	47 (13.7)
Gave up visiting specialists due to economic difficulties, n (%)	19 (3.7)	18 (3.8)	9 (3.4)	46 (3.7)
Mobility difficulties in visiting specialists, n (%)	28 (27.7)	76 (56.7)	88 (82.2)	192 (56.1)
Transportation difficulties in visiting specialists, n (%)	13 (12.9)	25 (18.7)	36 (33.6)	74 (21.6)
Needed more visits to specialists but could not get appointments	26 (4.6)	15 (4.4)	10 (8.2)	41 (5.1)

In the Table it is shown that the most significant barrier for patients of any age group is the decreased mobility, which is a bright manifestation of senile asthenia in daily life.

Special attention should be given to assessment of how mental health of an elderly patient influences accessibility of medical aid. An Australian research (4,967 patients older than 55 years) has shown that mental disorders significantly increase the risk of daily discrimination of elderly patients, especially in healthcare [30]. The risk of improper care in patients with mental disorders was 2–3 times higher than in their peers without mental problems.

ETHICAL RECOMMENDATIONS FOR ELDERLY PATIENT MANAGEMENT

By interpreting the basic ethical principles of management of elderly and senile patients, it is necessary to respect independence of patients, their well-being and justice regarding the possibility of obtaining qualitative medical aid as compared with other age groups. Doctor-patient relationships are essential for successful data collection, diagnostics and and choosing of a treatment plan. A doctor and a patient need to build up partnership relations with a high level of trust and confidentiality. Communication with an elderly patient should include explanation of treatment objectives and actions required to achieve the objectives. A doctor should honestly and in plain language explain the prognosis and outcomes expected when patients obtain or do not obtain treatment. In case of unfavorable prognosis, for instance, in oncological diseases, the issue should be treated on an individual basis taking into account mental characteristics of the patient, cognitive abilities, educational level and other factors that can influence perception of similar information.

Cognitive abilities of an elderly patient should possibly be estimated using specialized tests and with involvement of specialists, if necessary. While taking a decision about getting medical aid on the outpatient or hospital basis, it is necessary to consider not just the data about the patient's competence, but also whether he/she stays with other people who can take care of the patient and control treatment adherence. It is essential to assess health of caregivers, especially the ones who provide care for patients with severe somatic diseases (for instance, cancer, cardiac insufficiency), mental disturbances and mental deficiency. They should be provided adequate medical aid as well, if needed.

Decreased quality of medical aid given to an elderly patient, especially the one with cognitive disorders, can result from a lack of time for full communication and necessary examination, which is both an ethical, administrative and institutional issue. With rapid population ageing, certain standards should be reviewed (time spent on examination of one patient, number of doctors and nurses at outpatient medical institutions and hospitals). Healthcare institutions should currently be elderly patient-oriented.

With limited healthcare resources, the principle of equity in medical care given to elderly patients is commonly not followed. To overcome the barrier, the patient should be given care and observation at specialized therapeutic institutions, gerontological centers, it is also necessary to attract additional employees, including caregivers. It is desirable to have a constant treating physician who is aware of clinical, social and demographic characteristics of the patient and who managed to establish a contact with him or her.

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THE ETHICS OF DEPRESCRIBING IN OLDER ADULTS

Zyryanov SK, Baibulatova EA ✉

Peoples' Friendship University of Russia (RUDN University), Moscow, Russia

Older adults consume a disproportionate amount of medicinal products. Polypharmacy may increase the risk of adverse effects, result in poor medication adherence and unfavorable outcomes. There is considerable evidence that older adults are prescribed unnecessary or excessive medications. Treatment outcomes can be improved owing to controlled discontinuation of medicinal products. The deprescribing principles include analysis of all current prescriptions, detecting the medications that must be discontinued, dosage replacement or reduction, discussing the deprescribing regimen together with a patient, patient's control and support. Clear comprehension of indications and benefit of the conducted pharmacotherapy, objective risk assessment by prescribing physicians and by a patient, and a deliberate deprescribing plan can improve treatment outcomes of the elderly.

Keywords: polypharmacy, older adults, controlled withdrawal of medicinal products, drug therapy optimization

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✉ **Correspondence should be addressed**: Elena A. Baibulatova
ul. Miklukho-Maklaya, 6, Moscow, 117198, Russia; baybulatova-ea@rudn.ru

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ЭТИКА ОТМЕНЫ ЛЕКАРСТВЕННЫХ СРЕДСТВ У ПОЖИЛЫХ ЛЮДЕЙ

С. К. Зырянов, Е. А. Байбуталова ✉

Российский университет дружбы народов (РУДН), Москва, Россия

Пожилым людям назначается непропорционально большое количество лекарственных препаратов. Полипрагмазия увеличивает риск побочных эффектов, способствует снижению комплаентности и может привести к развитию неблагоприятных исходов. Имеются значительные доказательства неуместного, а также чрезмерного назначения лекарственных препаратов пожилым людям. Результаты лечения могут быть улучшены за счет контролируемой отмены лекарственных средств. Принципы отмены назначения включают анализ всех текущих назначений, определение препаратов, которые необходимо отменить, заменить или уменьшить дозу, планирование режима отмены назначения в партнерстве с пациентом, контроль и поддержка пациента. Четкое понимание показаний к назначению и пользы от проводимой фармакотерапии, а также объективная оценка риска врачами, назначающими лекарственные препараты, и пациентом, продуманный план отмены назначений могут улучшить результаты лечения пожилых людей.

Ключевые слова: полипрагмазия, пожилые люди, контролируемая отмена лекарственных средств, оптимизация лекарственной терапии

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✉ **Для корреспонденции**: Елена Александровна Байбулатова
ул. Миклухо-Маклая, д. 6, г. Москва, 117198, Россия; baybulatova-ea@rudn.ru

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Polypharmacy, which is the simultaneous use of multiple medications (M) [1], is very common. Recent analysis has shown that 25 to 40% of adults older than 65 years are prescribed at least five M [2]. Using most of the M can be considered inappropriate [3]. Though older adults can gain benefit from multiple M, inappropriate polypharmacy, where harm outweighs the benefit, can constitute significant risks and losses both for an older adult and for the entire society. In fact, inappropriate polypharmacy can result in adverse reactions, drug-drug interaction, hospitalization and, rarely, lethal outcome. Cumulatively, inappropriate polypharmacy represents a unique dilemma regarding a balance of benefit to harm, autonomy and justice [4].

The term 'deprescribing' first appeared in literature in 2003 [5]. Due to the growing global concern about negative consequences of excessive use of some M, approaches to minimization of harm seek increasing attention. The focus shifts from prescribing, which is traditionally the beginning of administration or restarting of a M, to deprescribing, especially with age. Deprescribing was defined as 'discontinuation of an inappropriate M under supervision of a medical professional to manage polypharmacy and improve outcomes' [6]. Dose reduction and transition to safer M are also discontinuation strategies, which are still effective when harm is minimized. The term 'inappropriate M' denotes a medicine, benefits of which outweigh its known risks. These are medicines with a high risk of causing harm, unnecessary or ineffective medicines, the ones that do not correspond to treatment objectives (for instance, products for prophylactic use among palliative care patients) or values and preferences of a patient, and the ones, the use of which is too burdensome [7]. It should be noted that 'medication discontinuation' is significantly different from noncompliance with prescribed medication or noncompliance with the treatment dosage regimen. Both medication prescribing and deprescribing should be done by a medical professional with an equal level of knowledge and attention.

Polypharmacy and use of potentially inappropriate products are associated (based on the data of some observational trials) with some negative health effects, including a decreased quality of life, side effects, falls, regimen noncompliance,

Table 1. Deprescribing context: examples of clinical, psychological, social, financial and physical factors that need to be considered in deprescribing [4]

Factors	Remarks
Clinical factors	Potential benefit associated with administration of M as compared to harm; a number of patients who require treatment; expected time to benefit; life prognosis; types of medicines (for instance, prophylactic or symptomatic treatment); physician who prescribed the M for the first time; presence/absence of triggers; presence/absence of symptoms; available alternatives (including non-drug methods of treatment); skills/knowledge/trust in physician; available evidence; ethical standards; healthcare system (high or low level)
Psychological factors	Ideas of health/attitude to medication therapy and diseases; cognitive distortions; cognitive functions; medical and medicinal literacy; knowledge; health and therapy objectives; mental health problems; survival strategy, personal preferences as far as health consequences go; relief of symptoms; preserved physical, mental and social activity; disease prevention; prevention of unfavorable outcomes/side effects; self-efficacy; wishing to participate in decision taking.
Social factors	Influence of a family and friends; social support/loneliness; burden of using multiple medicines/being a patient; performing a duty of a grandmother/grandfather; living conditions/real-life situation
Economic factors	Presence/absence of medical insurance; cost of medicines; economic expenses associated with polypharmacy/ occurrence of adverse drug reactions; available resources
Physical factors	Tablet burden; difficulty with medication (for instance, tablet swallowing); getting repeat prescriptions, managing remaining medications; adverse drug effects; general well-being; activities of daily living; quality of life (QoL)/self-reported health; concomitant diseases

Table 2. Principles of deprescribing in clinical practice [13]

Factors that influence deprescribing	Remarks
General practitioners are the key drivers of deprescribing as they produce a great effect not only on prescription, but also on perception and decisions of patients regarding medical care	– General practitioners (GPs) should be aware of their influence and be ready for a patient's resistance. – GPs should be provided better support to make deprescribing in general practice possible
The deprescribing process	– Discussion should be held between a medical professional and a patient/caregiver. – Explain why the medication should be discontinued, whether any constant benefit and long-term harm are available and why the medication can't be used for treatment any longer. – Patients and caregivers are ready for observation and expect to be informed by a medical professional what they should pay attention to and do if their condition is changed. – It should be stressed that the deprescribing is experimental
If a patient/caregiver resists termination of treatment	– Subsequent treatment will reveal why they are hesitating (for instance, previous experience). – Taking joint decisions is necessary to get a favorable outcome and support doctor-patient relationships

hospitalization and lethal outcome [8, 9]. For instance, *Passarelli et al.* [10] have found that an older patient who was prescribed a potentially inappropriate medical product can twice as likely have an adverse drug reaction as compared with an older patient who didn't take a potentially inappropriate medical product. It is believed that harm can be decreased if the dose is reduced, inappropriate M are discontinued and administered medicines are minimized. However, the potential benefit can be balanced with any risks that can arise due to discontinuation of M.

Regular review of medication therapy and discontinuation (controlled discontinuation) of inappropriate M are components of an optimal medical aid provided to the elderly (Tab. 1). It can lead to advantages including prevention of side effects, better treatment adherence and reduction in expenditure [11]. In practice, however, there exist many obstacles to deprescribing.

Four principles of biomedical ethics such as

1) benefit,
2) no harm,
3) autonomy,
4) justice

should be followed by deprescribing physicians in older adults.

Taking deprescribing as an action rather than inaction creates stronger moral obligations. It can also be due to the fear of negative consequences, which prevents deprescribing [12] (Tab. 2).

Comprehending a patient's experience is the principle of prescribing optimization and taking joint decisions [14]. Taking joint decisions is promoted not because it is acceptable from an ethical point of view and constitutes a patient's right, but because it can prevent a waste of time, resources and medications, and improve medication adherence and treatment outcomes [13, 15].

It is difficult to respect autonomy of older adults as they may not want active participation in taking decisions; their cognitive function can be impaired and family members will probably interfere in the process.

People are rarely informed about changes in risks and advantages of long-term administration of drugs with ageing. Refusal from inappropriate medications has a major financial benefit for a human being and the entire society. However, the principle of justice also means implementing equal rights irrespective of age [12].

CONCLUSIONS

Withdrawal of inappropriate medicinal agents can be a better clinical decision. It can result in significant clinical advantages, including a decreased number of falls. The basic reasons for medication discontinuation among the elderly can include a decreased risk of adverse effects, reduced probability of drug interaction and easier prescription regimen.

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CERTAIN ISSUES OF MEDICAL AND ECONOMIC EFFECTIVENESS OF TREATMENT OF ORPHAN DISEASES

Fokina DS[1] ✉, Zhukova OV[1], Grekhov AV[1], Khokhlov AL[2]

[1] Privolzhsky Research Medical University, Nizhny Novgorod, Russia

[2] Yaroslavl State Medical University, Yaroslavl, Russia

A lack of the single criterion for classifying rare diseases as a group of orphan diseases is the main current problem. First, it is associated with rare detection of symptoms among patients, especially children. Second, specialists have a limited number of methods of detecting orphan diseases. As the disease is considered rare, it is not profitable for pharmaceutical companies to produce the preparations which are purchased not in large numbers, but in single packages, because expenses on clinical trials and marketing advertising exceed return of investment. The market of orphan drugs in Russia is at the stage of development and formation. Medical organizations that carry out medicinal therapy of patients with orphan diseases require a clear set of regulatory documents ensuring provision of medical and pharmaceutical aid. Special attention should be paid to drawing up the lists of medicinal preparations to treat the patients. Personified accounting of patients with detected orphan diseases is an important stage for medical and pharmaceutical organizations. Modern diagnostics of orphan diseases at early stages, especially in children, exploration of specialized genetic methods of research and making them accessible for the population constitute an essential problem.

Key words: orphan diseases, rare diseases, clinical and economic method, drug provision, treatment problems, burden on the budget

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✉ **Correspondence should be addressed:** Daria S. Fokina
Minin and Pozharsky Sq., 10/1, Nizhny Novgorod, 603005, Russia; dsfokina4@mail.ru

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НЕКОТОРЫЕ ПРОБЛЕМЫ МЕДИКО-ЭКОНОМИЧЕСКОЙ ЭФФЕКТИВНОСТИ ЛЕЧЕНИЯ ОРФАННЫХ ЗАБОЛЕВАНИЙ

Д. С. Фокина[1] ✉, О. В. Жукова[1], А. В. Грехов[1], А. Л. Хохлов[2]

[1] Приволжский исследовательский медицинский университет, Нижний Новгород, Россия

[2] Ярославский государственный медицинский университет, Ярославль, Россия

В настоящее время основной проблемой остается отсутствие единого критерия отнесения редких заболеваний к группе орфанных заболеваний. Во-первых, это сопряжено с редким выявлением симптомов у пациентов, в особенности у детей. Во-вторых, специалисты располагают ограниченным числом способов определения орфанных заболеваний. Так как заболевание считается редким, фармацевтическим компаниям не рентабельно производить препараты, которые покупаются не массово, а единичными упаковками, затраты на клинические исследования, маркетинговые компании превышают их окупаемость. Рынок орфанных лекарственных препаратов в России находится на стадии развития и формирования. Для медицинских организаций, проводящих лекарственную терапию больных с орфанными заболеваниями, требуется четкий комплекс нормативно-правовых документов, обеспечивающих порядок оказания медицинской и фармацевтической помощи. Особое внимание должно быть уделено определению перечня лекарственных препаратов для лечения таких больных. Для медицинских и фармацевтических организаций важным этапом является проведение персонифицированного учета больных с выявленными орфанными заболеваниями. Важной проблемой является своевременная диагностика орфанных заболеваний на ранних стадиях, особенно у детей, освоение специальных генетических методов исследования и обеспечение их доступности населению.

Ключевые слова: орфанные заболевания, редкие заболевания, клинико-экономический метод, лекарственное обеспечение, проблемы лечения, нагрузка на бюджет

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✉ **Для корреспонденции:** Дарья Сергеевна Фокина
пл. Минина и Пожарского, 10/1, г. Нижний Новгород, 603005, Россия; dsfokina4@mail.ru

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In the modern world, a term of orphan (rare) diseases attracts more and more attention. An orphan disease includes life threatening or steadily progressive diseases detected with a low frequency, which, if the treatment is lacking, can result in a lethal outcome or disability. In the Russian Federation, orphan diseases include pathologies with an occurrence rate of 1:10,000 and rarer [1].

Orphan diseases are common among a small proportion of human population. A low number of these patients makes it difficult to examine and comprehend the course of such diseases. Patients, their family members and medical community are often deprived of complete information support [1]. Adoption of Federal Law No. 323-FL as of November 21, 2011 'On the basis of the protection of public health in the Russian Federation' was an important step. It contains a criterion of rare diseases such as the prevalence rate (at least 10 cases per 100,000 of people). The Law also regulates provisions about pharmacological support of citizens with diseases included into the list of life-threatening and chronic progressive rare (orphan) diseases, which can lead to reduced life expectancy or disability [2].

A list of rare diseases is formed by the Ministry of Health of the Russian Federation and published on the official site

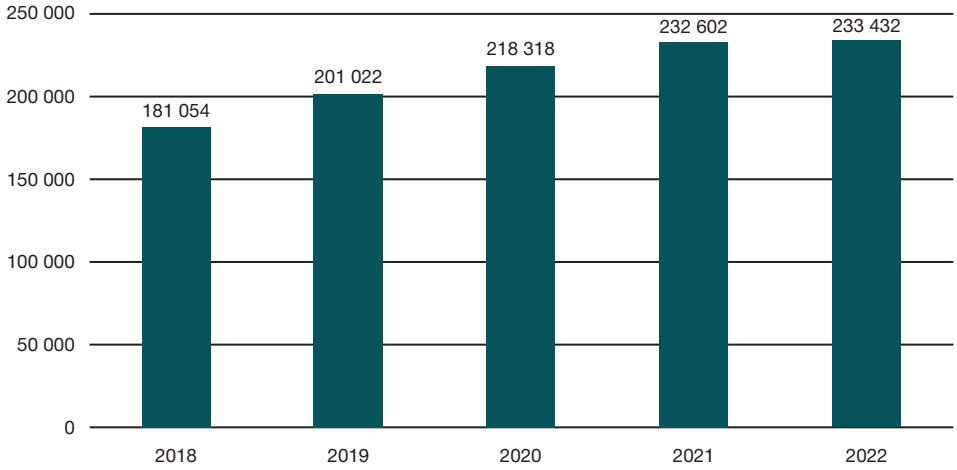

Fig. 1. Total number of patients within the High-Cost Nosologies register

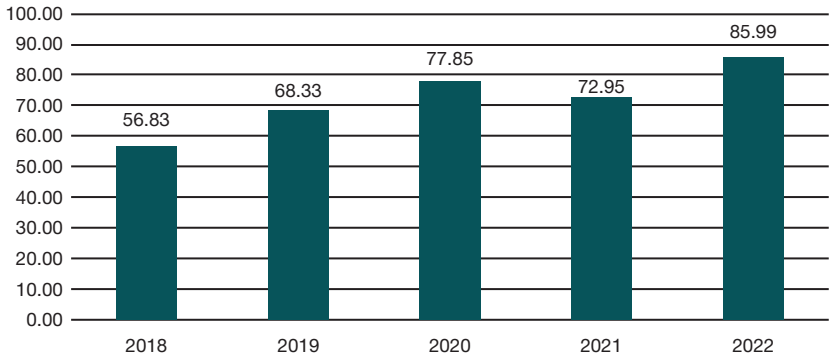

Fig. 2. Total cost of therapy, bln RUB

hereof. The list of 24 life-threatening and chronic progressive rare diseases included those with pathogenetic treatment with proven effectiveness. Such patients should be provided medicinal preparations for free. Moreover, treatment of hemophilia, cystic fibrosis, Gaucher disease and pituitary dwarfism has been financed by the '7 nosologies' state program since 2008; 7 other rare diseases have been added hereto over the last years [3].

Globally, the issue of orphan diseases has gained an increased attention lately. Specialized measures to ensure the rights of patients with orphan diseases have been applied: novel genetic concepts that prevent a disease and methods of diagnostics and treatment have been developed (orphan diseases are commonly of genetic nature). Patients are highly dependable on social, political and technological steps of a society [1].

Decision on how much the society should spend on researches of orphan agents is an ethical dilemma. On the one hand, every orphan nosology is just a small number of persons within the legal and political competence of a society. Investment of significant funds of the country into orphan diseases can be non-ethical from the utilitarian point of view, as it fails to display benefit for the society, and its alternative expenses are important from the perspective of opportunities lost for others. On the other hand, many people assert that the society has a moral obligation to help people who suffer from a serious but rare disease with no existing therapy. Moreover, medicine has a professional obligation to promote scientific knowledge in the area of novel methods of treatment. The contradicting moral obligations require totally different levels of funding of researches and developing orphan medications [4, 5].

Review of current social practices, regulatory approaches to solving the ethical and philosophical funding issue and treatment of orphan diseases, genetization tendencies is essential for the modern world as it ensures health protection rights.

The research objective is to determine the economic burden on support of patients with orphan diseases.

Systemic analysis to structure the cited data was selected as a method; the data of the Federal State Statistics Service were used as materials.

RESEARCH RESULTS

Patients commonly treat orphan diseases during the entire life. Huge load on the state budget is associated with a high cost of therapy, lack of innovative medical preparations and technologies that make therapy possible, rather high cost of therapeutic and rehabilitation activities [1]. The territorial entities of the Russian Federation face serious financial obligations regarding provision of their citizens who have rare diseases with orphan medicines [4, 6].

It is important to notice that a total number of patients within the '14 Nosologies' register is increasing on the annual basis. Their number increased by 28.93% during the last five years; thus, therapy of these patients requires better funding (fig. 1) [5, 6].

The key indicator to estimate the use of budgetary funds within the '14 Nosologies' program is represented by the use of funding in accordance with an increase of the total number of patients who obtain therapy as per the high-cost nosology. In 2018, the state allocated 56.83 bln RUB on this group of diseases, whereas in 2022 the funding increased by 1.5 times up to 85.99 bln RUB (fig. 2) [5, 6].

It should be noted that an increased funding of therapy of adults and children has been observed in the structure of

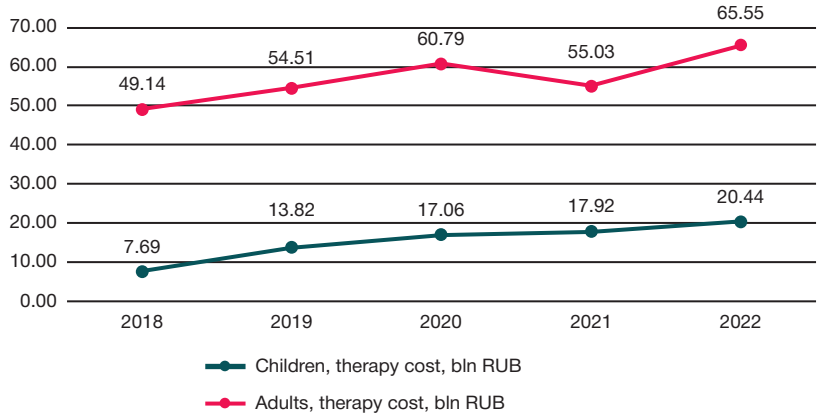

Fig. 3. Expenses on therapy of high-cost nosologies, bln RUB

the total therapy cost within the last five years [5, 6]. In 2018, 13.53% of all allocated budgetary funds were spent on pediatric therapy, whereas by 2022 funding of the patients was increased by 23.77% of the total treatment cost (Fig. 3).

DISCUSSION OF RESULTS

The most widely spread method of treatment of orphan diseases is based on achievement of health benefits considering the singe index, which unites life expectancy and health-related quality of life such as quality-adjusted years of life or disability-adjusted years of life [7].

Patients with orphan diseases require constant treatment and support of life quality. However, as there are few patients compared with a general number of patients, a limited number of resources will be allocated per their disease to make the society more useful.

Uncertainty about benefits belongs to a resource-allocating problem. During economic assessment, cost and benefit uncertainty can be taken into consideration when sensitivity is analyzed. Considerable amount of money is invested into research and developments for every new chemical object, though only one of 10 developed pharmaceutical compounds is successfully sold out in the market. In its turn, testing of orphan preparations is complicated due to a shortage of patients with a disease [2]. The geographic spread of such people on a large territory constitutes a big problem in treatment of these patients. It hampers their concentration within the same specialized medical institution, where qualitative aid could be provided [8].

Patients with orphan diseases often can't implement their right for drug support as the medication has not been developed or registered in Russia yet. As drugs are usually very expensive, the state can't provide full reimbursement. Normal financing of drug supply of patients with an orphan pathology at the expense of public resources frequently hampers treatment of patients [8].

The system of preferential provision of medicines is based on state guarantees of supply of preferential or free medications for separate categories of population. The following types of preferential medical assistance are set by the state depending on belonging to the category of citizens entitled to receive state social assistance as a set of social services and group of population, the outpatient treatment of which requires dispensation of medicinal preparations and medical devices by medical prescription free of charge or with 50% discount; citizens who have certain diseases (orphan diseases, high-cost nosology) [9].

The task concerning supply of patients with orphan diseases with medicinal preparations should be solved considering the conditions of provision of medical aid to various categories of patients. In the Russian Federation, subjects in the sphere of healthcare and pharmaceutical service management organization are significantly independent when drug support of population of the subjects of the RF is provided and when budgetary means are allocated to implement various programs. Territorial programs of state guarantee of provision of medical aid and drug support of population are valid at the regional level [10].

An important parameter of pharmacoeconomic effectiveness of using a medicinal agent for therapy of orphan diseases is represented by the 'threshold of payment ability'. If introduction of a new technology into treatment does not require additional expenses and even cuts expenses, the new technology is value-for-cost. But when additional means should be spent to achieve treatment benefit, the results do not allow to estimate readiness of population to pay for the therapy.

In the Russian Federation, there are three basic directions of preferential medicinal aid: provision of preferential categories of citizens with necessary medicinal preparations within a set of social services established in Federal Law as of July 17, 1999 No. 178-FZ 'Concerning state social aid'; drug supply of separate groups of population is provided free of charge or on prescription with a reduction of price in accordance with decree of the Government of the Russian Federation as of July 30, 1994 No. 890 (regional programs of preferential provision of medicines) and provision of some categories of citizens with expensive medicinal preparations as per the approved list of diseases (program of '14 high-cost nosologies') and a new trend of preferential provision of medicines for patients with orphan diseases. The systems are characterized by focus on treatment or prevention of a disease and clear regulation of the activity of all participants of the process of state social aid in the form of pharmacological support. All trends are patient-oriented. Every patient who needs the medicinal preparation should obtain it irrespective of the place of residence, property and social status. All this results in better affordability of medicinal preparations at stages of provision of medical aid and reasonable use of allocated funds [11].

Another completely unsolved problem is represented by timely diagnostics of orphan diseases. It means development of the respective base of knowledge and adoption of special research methods, formation of the personnel system and availability of genetic research [1]. Insufficient information support of patients and doctors who fail to obtain sufficient scientific and medical data can hamper identification and development of the treatment strategy of an orphan disease.

In Russia, the market of orphan medicines is at the stage of development and formation. An important step of market development includes legislative adoption of such a notion as 'orphan medicinal preparations' intended for diagnostics or pathogenetic treatment of rare diseases [12]. To expand the assortment of orphan medicinal preparations, an accelerated procedure of medicine expertise is established (art. 26 of Law No. 61-FZ). It does not mean that requirements to safety and effectiveness are decreased, but denotes that the results of preclinical and clinical trials performed outside the Russian Federation are accepted, though in accordance with the rules of good laboratory and clinical practice. Effective agents for therapy of rare diseases emerged on the Russian pharmaceutical market owing to the accelerated procedure of registration of medicinal preparations for therapy of OD.

The following consistency can be reviewed: medicinal preparations for therapy of orphan diseases are put into civil circulation in the Russian Federation 2 years after the preparations reach the market [11].

Increasing attention is paid to review of orphan diseases globally from the pediatric point of view, as they are mainly diagnosed in 2/3 of cases in childhood and often result in a fatal outcome.

An important part of all preventive activities aimed at a decrease of genetic load of population is represented by prenatal diagnostics that allows to decrease the risk of giving birth to a child with congenital and hereditary diseases. Timely detection of hereditary diseases can currently be provided by neonatal screening, which is considered as a basic liability of the state healthcare system in developed countries. It is the most effective method of diagnostics and prevention of hereditary diseases. It can be used to detect a pathology and determine the genetic risk of a hereditary disease for relatives of diagnosed infants. During the last decade, all newborns in the Russian Federation undergo neonatal screening for 5 hereditary diseases. The diseases can be diagnosed at the first screening stage without molecular and genetic researches. However, subsequent confirming molecular and genetic diagnostics that predicts the severity of clinical manifestations and corrects treatment is required taking into account the variability of a clinical picture in different mutations of the same gene. According to the Ministry of Health of the Russian Federation, diseases annually included into the screening program are diagnosed in 1,200 newborns in average [3].

Information of a patient about the results of diagnostics is always complicated and associated with potential traumas. Thus, an urgent task includes building forms of social interaction with parents and pediatric patients and searching for ways to inform the society of orphan diseases [1]. Limited effectiveness of exact diagnostics of orphan diseases at the level of the primary link and at hospitals, absence of developed medical standards of treatment for some nosological forms, poor availability of specialized treatment for orphan patients in subjects of the Russian Federation can impair specialist-patient communication.

Patients with orphan diseases increasingly act as a classic example when the phenomenon of biosociality is being analyzed [13]. Groups of patients with orphan diseases by certain nosologies are formed, global support centers for all orphan diseases can be organized. The issue results in new forms of sociality where people are brought together and united owing to their life experience and struggle with a disease caused by certain genetic mutations. Moreover, the communities are formed on the basis of a pronounced interest of pharmaceutical companies, which commonly initiate development of medicinal preparations for various groups of patients who organize different activities devoted to orphan diseases [1].

CONCLUSIONS

Ethical aspects of prioritizing research financing do not always constitute the main issue of discussion. Assigning a legal status to orphan diseases means an undoubted progress both for medical law and for bioethics. Just distribution of resources in healthcare is still limited with the existing methods of treatment. The issue of necessary integration of knowledge, plans and researches by orphan diseases arises at the international level. Then common efforts would be coordinated and the process of etiology cognition, prevention and treatment of orphan diseases, their statistical processing, development of screening systems of diagnostics and informational aid for doctors and patients will be developed.

During the neonatal period, suitability of a wider screening for congenital and inherited metabolic diseases, and the most widely spread nosological forms of rare diseases, in particular, is not doubtful. All these conditions can be detected in the neonatal period. This will prevent severe disability of sick children reducing a number and duration of hospitalization until their transfer to outpatient treatment.

Investment into research of rare diseases offers hope to those in need and potential benefits for the future generations. The principle supports a stronger role of the state sector in taking decisions about the priority of financing the studies of orphan medicinal preparations.

Applying traditional economic assessment to therapy of orphan diseases will likely be unsuccessful, as maximization of global healthcare with national funds of separate countries will not be politically acceptable in either country.

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THE TROUBLE WITH ANTIBIOTICS

Palyutin ShKh ✉, Zilber IE, Pozdnyakov NO, Sinitsina OA, Speshilova SA, Sirotkina AM

Yaroslavl State Medical University, Yaroslavl, Russia

During the long history of antibiotics, resistance of causative agents of main infectious diseases was estimated as a very serious threat to effective treatment of patients and as a social and economic problem faced by the entire mankind. The activities performed by the medical society provided no significant effect resulting in growing antibiotic resistance. The pandemic of novel coronavirus infection only made things worse. It became a new challenge for the medical community regarding searching solutions which are clinical, organizational and methodological by nature in the global struggle with resistance to antibiotics. The reviews of several studies of coronaviral infections have shown that treatment with antibiotics failed to correlate with the decreased all-cause mortality. In this work, we have reviewed some aspects of therapy with antibiotics, including ethical ones. Ethical aspects of antibiotic therapy concern decisions of physicians about administration of commonly unnecessary antimicrobial agents.

Keywords: antibiotics, antibiotic resistance, antibiotic therapy, COVID-19, ethics

Author contribution: Speshilova SA — research planning, data collection, data analysis, data interpretation, preparing a manuscript draft, article concept, literature selection and analysis, data generalization, text writing; Sinitsina OA — research planning, data selection and analysis; Demarina SM — preparing a list of literature; Palyutin ShKh — literature selection and analysis, data generalization, text writing.

✉ **Correspondence should be addressed:** Shamil Kh. Palyutin
ul. Revolutsionnaya, 5, Yaroslavl, 150000, Russia; shamico@yandex.ru

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ПРОБЛЕМЫ АНТИБИОТИКОТЕРАПИИ

Ш. Х. Палютин ✉, И. Е. Зильбер, Н. О. Поздняков, О. А. Синицина, С. А. Спешилова, А. М. Сироткина

Ярославский государственный медицинский университет, Ярославль, Россия

На протяжении всей истории применения антибиотиков риск развития устойчивости возбудителей основных инфекционных заболеваний оценивался как очень серьезная угроза для эффективного лечения пациентов и, в целом, как социально-экономическая проблема для всего человечества. Принимаемые медицинским сообществом меры не давали значимого эффекта, рост антибиотикорезистентности продолжался. Пришедшая пандемия новой коронавирусной инфекции лишь усугубила ситуацию и стала новым вызовом для медицинского сообщества в плане поиска решений как клинического, так и организационно-методического характера в борьбе с устойчивостью к антибиотикам, получившей глобальное распространение. В обзорах, включавших несколько исследований по коронавирусной инфекции, было продемонстрировано, что лечение антибиотиками не коррелировало со снижением смертности от всех причин. В данной работе рассмотрены некоторые аспекты проведения антибиотикотерапии, в том числе этического характера. Этические аспекты назначений антибиотикотерапии касаются решений врача о назначении конкретному пациенту антимикробных препаратов, в которых очень часто нет никакой необходимости.

Ключевые слова: антибиотики, антибиотикорезистентность, антибиотикотерапия, COVID-19, этика

Вклад авторов: С. А. Спешилова — планирование исследования, сбор данных, анализ данных, интерпретация данных, подготовка черновика рукописи, концепция статьи, подбор и анализ литературы, обобщение информации, написание текста; О. А. Синицина — планирование исследования, сбор данных, анализ данных; Е. Г. Лилеева — концепция статьи, подбор и анализ литературы; С. М. Демарина оформление списка литературы; Ш. Х. Палютин — подбор и анализ литературы, обобщение информации, написание текста.

✉ **Для корреспонденции:** Шамиль Хусяинович Палютин
ул. Революционная, д. 5, г. Ярославль, 150000, Россия; shamico@yandex.ru

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I. USE OF ANTIBIOTICS IN THE COVID-19 ERA.

Years of the COVID-19 (*COronaVIrus Disease 2019)* pandemic exacerbated the problem of antibiotic resistance and rational use of antibiotics in clinical practice even more. Until the pandemic, the level of antibiotic resistance of some infectious agents, especially nosocomial infections, raised very serious concerns of the world medical community. Let's remember a famous report of a group of English economists headed by J. O'Neill [1, 2], made for the government of the Great Britain. In that report, an increase of lethal outcomes due to resistance of challenging causative agents from 700 thousand to 10 million a year was predicted by 2050. Negative trends of increased resistance of basic clinically significant causative agents were noted even within community-acquired flora.

Some people believed that these figures were slightly exaggerated [3].

However, another data analysis was performed in 2019 to examine antibiotic resistance and its effect on healthcare in 204 countries [4]. The figures predicted by a team of English economists in 2014 will be presented much earlier.

4.95 million lethal outcomes associated with bacterial resistance in 2019, including 1.27 million attribute-based outcomes, were determined in a novel study. In 2019, lower respiratory tract infections included over 1.5 million resistance-associated lethal outcomes, which turns them into the most severe infectious syndrome. In 2019, six leading lethal antibiotic-resistant pathogens (*Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*) were

attributively responsible for 929,000 deaths and associated with 3.57 million lethal outcomes. A pathogen/medicinal agent (MRSA) combination resulted in over 100,000 lethal outcomes associated with antibiotic resistance in 2019. Six more similar combinations were the reasons for 50,000–100,000 deaths each: multidrug resistant tuberculosis, excluding extensively drug-resistant tuberculosis, third generation cephalosporin-resistant collibacillus, carbapenem-resistant *A. baumannii*, fluoroquinolone-resistant collibacillus, carbapenem-resistant *K pneumoniae* and third generation cephalosporin-resistant *K pneumoniae*.

The SARS-CoV-2 (severe acute respiratory syndrome-related coronavirus 2) pandemic, high incidence of COVID-19 and an associated round of excessive and unjustifiable administration of antibiotics brought medicine even closer to the postantibiotics era, according to many experts.

The analyses devoted to the strategy of using antibiotics in case of novel coronavirus were published in 2020–2022. It has been confirmed that bacterial involvement is not that large. Thus, a wide use of antibiotics in this pathology is not justified. For instance, in a significantly characteristic review that included 19 studies [5] it has been demonstrated that the secondary or concurrent infection (coinfection) was confirmed in 17.6% of patients only with the level of antibiotics administration being 74%. Meanwhile, a half of those who used antibiotics were not related to the group of severe and critical patients. It has been noted that the signs that confirm accession of the secondary bacterial infection developed on days 14 and 17 after the diagnosis was made for those who survived/failed to survive respectively. An excessive strategy of early and unjust administration of antibiotics has been traced.

A work of famous Spanish investigators [6] has been released approximately at the same time. Its meta-analysis has shown that a bacterial or fungal infection was diagnosed only in 7–8% of hospitalized patients with COVID-19. The infections occurred more frequently among patients from the intensive care units (8–14%) as compared with patients from other departments (4–6%).

Coinfections were found in 3.5% patients only, with secondary infections occurring in 14.3%. Meanwhile, *Mycoplasma, Haemophilus influenzae и Pseudomonas aeruginosa* belonged to the most frequent bacterial concomitant microorganisms.

In spite of low registered levels of bacterial infections, the use of antibiotics among patients with COVID-19 was rather high: 71.9% of patients with COVID-19 were administered antibiotics. It should be noted that 74% of administered antibiotics belonged to third generation fluoroquinolones and cephalosporines.

In April 2021, researchers from Pakistan [7] analyzed data of 617 patients hospitalized with COVID-19. It has been established that 97.3% of patients were administered antibiotics on the examination day. The secondary bacterial infections or co-infection (concomitant infection in patients with COVID-19) developed in 1.4% of patients only. On the date of examination, one patient got 1.7 antibiotics and 85.4% of antibiotics were given for the purpose of prevention. Azithromycin (35.6%), ceftriaxone (32.9%) and meropenem (7.6%) were most commonly administered antibiotics.

Doubtful early use of antibiotics in patients with COVID was confirmed in LEOSS trial [8], when 3.627 cases that corresponded to all inclusion criteria (episodes from March 18, 2020 to February 16, 2021; age ≥ 18 years; data about antibiotic therapy; with a minimum observation period of 3 days (≥72 hours)) were registered. In addition to qualified cases, the ones with no documented treatment outcomes were excluded as well. Procalcitonin (PCT) was dichotomized with a threshold value commonly used for lower respiratory tract diseases. The value was equal to 0.5 ng/ml (≤0.5 ng/ml and >0.5 ng/ml). The clinical outcomes considered in this trial included all-cause mortality and progression to the next advanced phase of the disease as per the LEOSS regimen until the end of SARS-CoV-2 acute phase each (for instance, convalescence or death).

When the primary endpoint was estimated, the authors have decided that treatment with antibiotics failed to correlate with a decreased all-cause mortality or transition to the next, more advanced (critical) phase ($p > 0.05$ for both indicators). As far as the secondary endpoints go, patients who were administered antibiotics during a non-complicated phase showed a no less all-cause mortality irrespective of the PCT level and progressed at least to the next, more advanced (complicated) phase ($p > 0.05$). Patients with PCT > 0.5 ng/ml who were administered antibiotics during a complicated phase demonstrated a higher all-cause mortality ($p = 0.029$) with no significant difference in a possible progression to a critical phase ($p > 0.05$).

The authors conclude that the use of antibiotics in patients with SARS-CoV-2 wasn't associated with a positive effect on all-cause mortality or disease progression.

Physicians who actively prescribed and recommended antibiotic therapy during the first year of the pandemic were slightly trapped in terminology as the changes in the pulmonary tissue were estimated as 'pneumonia'. Incidence rate of pneumonia in Russia is reported, especially during the first year of the pandemic. In Russia, the Federal Service for Surveillance in Healthcare recorded 2.722,292 cases of community-acquired pneumonia in 2020 and only 760.074 cases in 2019. The growth accounted for 258%, making community-acquired pneumonia the leading cause of morbidity in Russia in 2020. In the future, a better comprehension of processes occurring in case of coronavirus infection was accompanied by a more responsible definition of pneumonia and administration of antibiotics.

The use of antibiotics is growing worldwide. However, the growth is associated with developing and actively developing countries (China, India, Russia) [9].

In this study, the tendencies and driving forces of using antibiotics from 2000 to 2015 were analyzed in 76 countries and the total global consumption of antibiotics until 2030 was predicted. From 2000 to 2015, consumption of antibiotics expressed as defined daily doses (DD) was increased by 65% and the level of antibiotic consumption was increased by 39%. In has been established in the report that the mean DDD per 1,000 citizens was about 20 per day in 2015.

The authors stated that a sharp increase of using of drugs of last resort such as glycylcyclines, oxazolidinones, carbapenems and polymyxins was of particular concern. As per the presented prognosis, the global consumption of antibiotics in 2030 will exceed the indicators of 2015 by 200%, in case of no changes in the policy.

A reasonable assumption can be made that years of the pandemic made antibiotic resistance worse and complicated the issue of selecting an adequate antibiotic by physicians.

The pandemic highlighted some interesting facts about how western and Russian physicians reacted to the situation. For instance, there was a 56% drop in administration of 10 most popular antibiotics in the outpatient setting during the first pandemic peak (1st half of 2020) [10]. In the USA, consumption of such medicinal preparations as azithromycin and amoxicillin [11] during the first months after the pandemic was reduced

by 64% and 63% respectively; April 2020 was compared with April 2019.

In Russia, the situation was slightly different. In October 2020, 9 professional medical communities released an appeal to Russian doctors [12]. It stated that a significant growth of sale of antibacterial medicinal preparations by pharmacies and their purchase by therapeutic institutions discovered against the background of novel coronavirus pandemic were of serious concern. According to some trials, over 90% of patients with COVID-19 were given antibiotics, including combined therapy and parenteral medicinal agents on the outpatient basis.

According to some authors, consumption of azithromycin and, to a lesser extent, of levofloxacin and amoxicillin/clavulanate in Russia was dramatically increased in 2020. Subsequently, organizational efforts of the Ministry of Health of Russia and expert community still resulted in an interrupted negative tendency. As pharmacy analysts state [13], the pharmacy market grew by 7% in January–November 2021 as compared with January–November 2020, and sales of antiviral and antibacterial medicinal preparations dropped. A decrease of sale of systemic antibacterial medicinal preparations by 10.2% was especially emphasized. This was associated with optimized medicinal expenses to treat coronaviral infection. It has also been noted that dispensation of the antibiotic most actively sold in 2020 (azithromycin) has been cut nearly in half in natural terms (by 42% in packs).

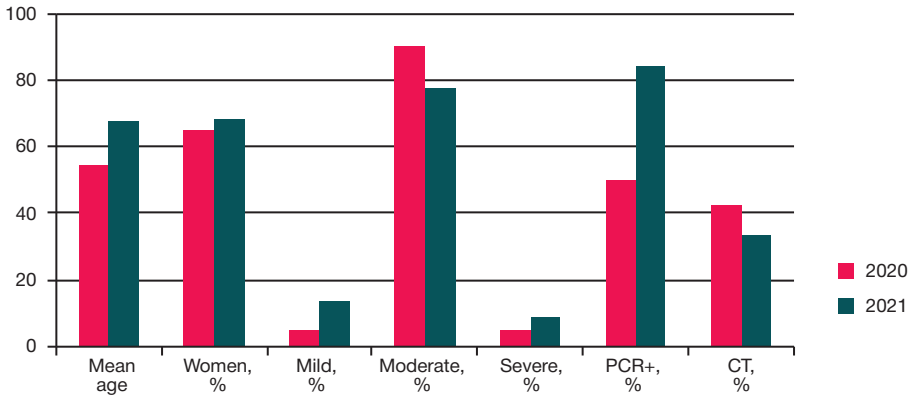
A positive decrease in excessive use of antibiotics in patients with coronavirus was noted only in some months after the pandemic when physicians came across the first analytical works devoted to management of patients with coronavirus pneumonia and the role of separate groups of medicinal preparations in the course of the disease, its complications, and decreased lethality.

Organizational aspects and extensive work of the Ministry of Health of Russia served its purpose as well. Activization of distance learning to some extent even simplified access to the latest data obtained by researchers from different countries.

The data are confirmed in our region as well. Case histories of hospitalized patients were analyzed in repurposed COVID hospitals.

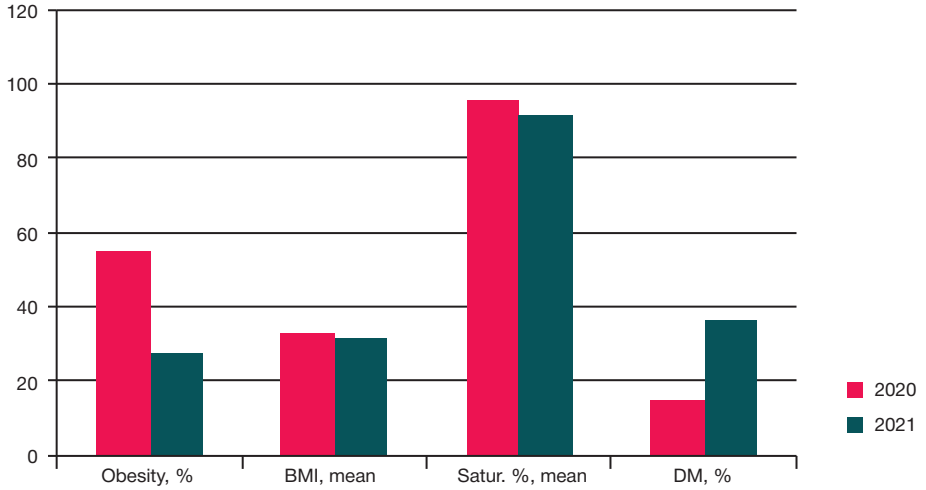
The repurposed department for patients with COVID-19 had two observational stages (February 2020 and February 2021). The object of observation included hospitalized patients (2020, n = 20; 2021, n = 22).

It should be noted that in 2021 the age of hospitalized patients was slightly increased and percentage of verified diagnosis of novel coronavirus was significantly increased (fig. 1). The patients had rather similar profiles in 2020 and 2021 (fig. 1, 2): women predominated among those who were admitted to the department. No significant difference was found in distribution of patients by the rate of severity. Percentage of patients with concomitant diabetes mellitus was increased (fig. 2).



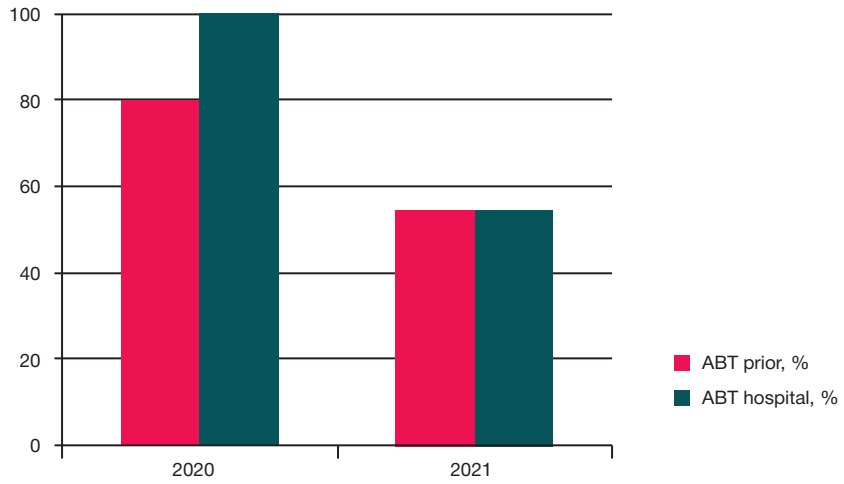
Notes: mild — mild course; mod. — moderate course, sev. — severe course; PCR+ — polymerase chain reaction, positive test for SARS-CoV-2; CT% — computed tomography, percentage of involved pulmonary tissue.

Fig. 1. Characteristics of patients included into analysis (I)



Notes: obesity — obesity was diagnosed based on the case history, BMI — body mass index; satur% — percentage of oxygen saturation (pulse oximetry); DM — diabetes mellitus.

Fig. 2. Characteristics of patients included into the analysis (II)



Note: — ABT prior,% — a share of patients who were given antibiotics on the outpatient basis prior to admission to the hospital; ABT hospital,% — a share of patients who were given antibiotics on the hospital basis.

Fig. 3. Use of antibiotics at the outpatient and inpatient stages (2020–2021)

In February 2020, 80% of patients included into the analysis were given antibiotics at the prehospital stage, whereas 100% of hospital-based patients were administered antibiotics starting from the first day (fig. 3). And this is the most important aspect of the topic discussed.

In February 2021, only 55% of patients with a history of outpatient antibiotic therapy were admitted to the department, and antibiotics were given to approximately 55% of hospital-based patients as well (fig. 3).

The global medical society has placed and is still placing great expectations in the program of control (or management) of antibiotic therapy still hoping for its effectiveness. In English literature, the program was called '*Antimicrobial stewardship*' (AMS). However, in the recent past, active implementation of these principles came across serious difficulties in real clinical practice. There existed objective and subjective reasons for that. According to authors of a work [14] devoted to this problem, the World Health Organization adopted a global plan of actions to combat resistance to antimicrobial medicinal agents including five basic objectives such as improved awareness of the society and suppliers of medical services, investment in diagnostics and therapy, update of epidemiological surveillance, prevention of infections and optimization of use of antimicrobial agents [15]. However, during the COVID-19 pandemic, more attention was given to the principles of management of antimicrobial medicinal substances (AMS), and their effect on the total resistance of pathogens was decreased [16]. Though the strategies were announced by the WHO in 2015, the emphasis of an increased attention of medical society on antibiotic resistance was not taken seriously even prior to the pandemic [17]. The fact is no less important.

II. ETHICAL ASPECTS OF ANTIBIOTIC THERAPY

Let's concentrate on several ethical aspects of antibiotic therapy including the issues of pharmacovigilance and actions of regulatory bodies and taking fluoroquinolones as an example. In the early days of the pandemic, levofloxacin was included into the risk group due to unreasonable use of antibacterial agents in COVID-19. Levofloxacin belongs to the so-called respiratory fluoroquinolones.

Grepafloxacin was the first respiratory fluoroquinolone in the Russian market. The medicinal agent was registered in the Russian Federation in 1997. In a year, the medicine was withdrawn from the market due to significant problems with cardiotoxicity (increase in QT interval) when even lethal arrhythmias were developed. In other words, the medical community realized the risks of therapy with fluoroquinolones. Cardiotoxicity was essentially a class effect typical of this group of preparations. In this regard, organizational solution of the manufacturing company seemed ethically logical. The company produced a novel and potentially effective medicinal agent. The agent was simultaneously registered in many countries. However, as soon as grepafloxacin-associated adverse drug reaction reports occurred, the company, having weighted the pros and cons, decided to withdraw the agent from all the markets approximately at the same time.

In the beginning of 2000, the leading experts were waiting for novel agents belonging to this group (gatifloxacin, in particular).

The history of gatifloxacin is unique in some way.

In the USA, gatifloxacin was registered by BMS in 1999.

In 2006, data about serious safety issues of gatifloxacin were published [18, 19].

In the Russian Federation, gatifloxacin was registered in 2009.

In 2019, the registration was cancelled. In letter of the Federal Service for Surveillance in Healthcare No. 02и-360/19 as of Febr. 08, 2019 [20], a history of gatifloxacin is described in detail: 'Having analyzed the international regulatory solutions, Bristol-Myers Squibb that developed Tequin (gatifloxacin) withdrew the medicinal agent from the market of the USA in 2006 due to the risk of dysglycemia.

Subsequently, FDA withdrew reproduced preparations of gatifloxacin from the market [21]. No data about registration of gatifloxacin systemic preparations in the EU, Canada and Australia were found during analysis of information obtained from the foreign regulatory agencies. In India, circulation of gatifloxacin preparations was terminated in 2011 [22].

Then a just question arises. Why gatifloxacin was still registered in the Russian Federation in spite of all 'shortcomings' that prevented its manufacture due to safety-related serious issues?

Of course, one can argue that the medicinal agent is still used in many countries, though in a limited way (only eye drops). Dysglycemic effects of gatifloxacin are not well explained yet (it causes both hypoglycemic and hyperglycemic episodes) and different adverse effects can be rarely found with the same preparation.

Ethical aspects refer to antibiotic therapy in general and solutions of a certain doctor about unnecessary use of antimicrobial drugs.

In conclusion, one can quote Jan Carlzon, a famous Swedish businessman: 'An individual without information can't take responsibility. An individual with information can't help but take responsibility'. Doctors all together and every doctor as an individual should take the responsibility for their solutions and risks associated with antibiotic therapy and antibiotic resistance.

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ETHICS OF RESEARCH PRACTICE IN CLINICAL MEDICINE

Ziganshina LE[1,2,3] ✉, Ziganshin AU[2]

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

[2] Kazan State Medical University, Kazan, Russia

[3] Peoples' Friendship University of Russia (RUDN University), Moscow, Russia

A half a century ago Archibald Cochrane, British physician and researcher, emphasized the necessity for critical assessment and a more elaborated approach to biomedical research results. Evidence-based medicine, which is designed to protect a patient from using scientifically unjustified technologies in healthcare, was widely developed subsequently. However, it soon became evident that numerous essential scientific researches contain a substantial proportion of costly but less informative and unjustified trials. They do not add any significant knowledge (wastes or unnecessary spending in research). In 2014, like-minded investigators have joined together in the international community of Evidence-based research. They suggested a plan of actions and algorithm for evidence-based research denoting the liability of all subjects. It is essential that the processes were under supervision of the scientific and medical society.

Keywords: clinical trials, novel medicines, Cochrane, ethics

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✉ **Correspondence should be addressed:** Liliya E. Ziganshina
ul. Barrikadnaya, 2/1, b. 1, Moscow, 125993, Russia; lezign@gmail.com

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ЭТИКА ИССЛЕДОВАТЕЛЬСКОЙ ПРАКТИКИ В КЛИНИЧЕСКОЙ МЕДИЦИНЕ

Л. Е. Зиганшина[1,2,3] ✉, А. У. Зиганшин[2]

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

[2] Казанский государственный медицинский университет, Казань, Россия

[3] Российский университет дружбы народов (РУДН), Москва, Россия

Полвека тому назад британский врач и исследователь Арчибальд Кокрейн выдвинул идею о необходимости критической оценки и более тщательного подхода к результатам биомедицинских исследований. Позднее широкое развитие получила новая парадигма — доказательная медицина (evidence-based medicine), которая призвана защитить пациента от применения научно необоснованных технологий в здравоохранении. Однако вскоре стало очевидно, что внутри большого массива важных научных исследований имеется значительная часть дорогостоящих, но мало информативных, необоснованных исследований, которые не добавляют каких-либо существенных знаний (отходы или пустые растраты в исследованиях). В 2014 г. исследователи-единомышленники объединились в международное сообщество Научно-обоснованных исследований и предложили план действий за научно-обоснованные исследования, их алгоритм, обозначив ответственность всех участников исследовательского процесса. Важно, чтобы эти процессы были постоянно под вниманием научного и медицинского сообщества.

Ключевые слова: клинические испытания, новые лекарства, Кокрейн, этика

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✉ **Для корреспонденции:** Лилия Евгеньевна Зиганшина
ул. Баррикадная, д. 2/1, стр. 1, г. Москва, 125993, Россия; lezign@gmail.com

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The idea that ethical principles regulate the rights of patients, potential risks for them associated with the use of various medical technologies (and interventions in general) and participation in clinical trials, rights of physicians who render medical assistance or participate in clinical trials performing various functions is customary and habitual for the medical community.

Clinical trials of effectiveness and safety of interventions (and medicinal products in particular) are traditionally taken as the fundamentals of evidence-based medicine. The paradigm of evidence-based medicine has brought a silent revolution in international healthcare since the Cochrane Collaboration was founded in 1993. It was developed to produce systematic reviews of clinical research results properly selected and critically assessed in accordance with healthcare problems of the previous century as viewed by Archibald Leman Cochrane (Archie Cochrane). His name was subsequently given to the Collaboration.

His fundamental legacy included a thought about the necessary provision of equal and just fair medical assistance using only the methods the effectiveness of which was proven in properly planned and conducted trials [1]. Archie Cochrane made a decisive contribution to the development of systematic reviews and randomized clinical trials as methodology assessing effectiveness of interventions and clinical epidemiology as science. In his legendary critical review he defined systematic reviews which started bearing his name soon: "*It is surely a great criticism of our profession that we have not organised a critical summary, by specialty or subspecialty, adapted periodically, of all relevant randomised controlled trials*" [2].

The simple principles formulated by A. Cochrane gained worldwide recognition, whereas Cochrane systematic reviews are recognized as a gold standard of high-quality scientific research even today [3].

In 1996, David Sackett who was a founder of the first Department of Clinical Epidemiology at McMaster University, developed the ideas and defined evidence-based medicine as '*the conscientious, explicit and judicious use of current best evidence in making decisions about the care of the individual patient*' [4]. It means medical practice where physicians use interventions (diagnostic, therapeutic, etc.) integrating individual clinical expertise, views and needs of their patients with the best available external clinical evidence from systematic research. Dr. Sackett warned his contemporaries that practice can rapidly be out of date to the detriment of patients if no modern or actual best proof (scientific research) are found.

But even then, it was obvious for founding fathers of evidence-based medicine that ethics of research practice in clinical medicine is coming to the foreground though attributes of ethical expertise of clinical trials including detailed informed consents are used [5]. In 1994, Douglas Altman, professor of medical statistics in Oxford University who was a pioneer of the Cochrane collaboration, wrote as follows: 'We need less research, better research, and research done for the right reasons. *What should we think about a doctor who uses the wrong treatment, either wilfully or through ignorance, or who uses the right treatment wrongly (such as by giving the wrong dose of a drug)? Most people would agree that such behaviour was unprofessional, arguably unethical, and certainly unacceptable. What, then, should we think about researchers who use the wrong techniques (either wilfully or in ignorance), use the right techniques wrongly, misinterpret their results, report their results selectively, cite the literature selectively, and draw unjustified conclusions? We should be appalled. Yet numerous studies of the medical literature, in both general and specialist journals, have shown that all of the above phenomena are common. This is surely a scandal'* [6].

Like-minded investigators of those years hoped that substantial implementation of methodology of systematic reviews and thorough critical assessment of research to include evidence in synthesis will be enough to overcome these problems. However, the scandal continued to worsen as soon as numerous trials and systematic reviews of doubtful quality appeared. This shows clear understanding of redundancy and uselessness of research in medicine and healthcare. The fact was most clearly expressed in a 2005 essay written by John Ioannidis, professor of Stanford University. He made a significant contribution to evidence-based medicine and clinical epidemiology examining own research practice in medicine and social sciences, being the founder of the so-called meta-research. His essay named 'Why most published research findings are false' [7] was the most read article in history of the Public Library of Science (PLOS) as of 2020 with more than three million of views.

The progressive medical and healthcare society has a perception of waste in research, which do not correspond to ethical principles of research practice. The ideas were clearly expressed in the background paper by Iain Chalmers and Paul Glasziou from the Center for evidence-based medicine of the Department of Medicine at the University of Oxford [8]. Sir Iain Chalmers is also a founder of the Cochrane Collaboration, the James Lind Library, the James Lind Initiative and Testing Treatments Interactive. The publication starts with citation of an investigator with myeloma published in the *British Medical Journal* [9]. He complains that the results of four randomized trials on his disease have not been published for several years since conference abstracts were presented. The citation is clear and representative. It states as follows: "*Research results should be easily accessible to people who need to make decisions about their own health. Why was I forced to make my decision knowing that information was somewhere but not available? Was the delay because the results were less exciting than expected? Or because in the evolving field of myeloma research there are now new exciting hypotheses or drugs to look at. How far can we tolerate the butterfly behaviour of researchers, moving onto the next flower well before the previous one has been fully exploited?"* [9].

I. Chalmers and P. Glasziou state [8] that waste in research and presentation of results are inevitable and tolerable. They brought together evidence from numerous research and revealed to the world the level of waste in research, which at least seems surprising.

The authors considered four stages of research and displayed cumulative losses expressed in monetary terms: dividends from research-invested tens of billions of dollars are wasted annually due to the problems that can be solved. The authors mention the problems and suggest solutions within the four stages of research, though a single simple solution is lacking. The solutions include selection of an incorrect research question; conducting unnecessary or poorly planned trials; unsuccessful timely publication of results or lacking publication; bias or useless result reporting (publications).

Though the authors were mainly guided by clinical trial design data, they assume that the problems can be applied to other medical trials as well. It is believed that the modest attempts to comprehend and improve the quality and methodology of research and publish the results would significantly increase the dividends i. e., benefit for patients and entire society. They recommend how to solve the problem and display the steps that have already been followed in Great Britain in this direction. Thus, the programs assessing medical technologies of the National Institute of Healthcare Research require or order (finance) systematic reviews prior to taking a decision about financing the primary trials, publish all research results in the form of online monographies, whereas all study protocols have been freely available since 2006.

Appeal of I. Chalmers and P. Glasziou that not just wasted investments but also a human being and human health are important were further developed in the concept of evidence-based research.

The concept and term 'evidence-based research' were accepted in 2009. It seemed to be redundant. The term was created to determine the focus area of a group of like-minded investigators who opposed a widely accepted practice of ignoring a set of results of earlier studies in favor of scientific interests and ambitions to the novel systematic approach of evidence-based research [10–18]. The concept means using systematic methods to search for and detect all previous trials for a specific research issue presenting references to earlier trials when novel trials are justified, developed and discussed. In other words, the essence of this approach consists in the obligatory use of systematic reviews, which have been either conducted or developed independently prior to any novel clinical trial.

It is essential, as numerous analyses of published trials to detect their possible belonging to wastes have shown that the ignoring is a common practice even among clinical trials published in most respected medical journals and considered as qualitative trials by their methodology [19–26]. In these publications, the authors ignore the systematic approach selectively citing earlier trials and being guided by own strategic intentions and preferences. This is basically a conflict of interests.

The research practice is a serious problem mainly due to the risks it bears in relation to prevented harm for study subjects. It is also a source of wastes.

To overcome the challenges, like-minded investigators have united in 2014 in Bergen, Norway, to create the international community of Evidence-based research (EBRNetwork, http://ebrnetwork.org). They developed a mission statement where their goal was formulated as 'No novel trial without a systematic review of existing evidence and effective development, renewal and distribution of systematic reviews' and offered a plan of actions for evidence-based trials and their algorithm denoting the liability of all subjects.

The application was published in the *British Medical Journal* in 2016 [27], and in the *Kazan Medical Journal* in 2019 (in Russian) [28] (translated by Cochrane, Russia). Initially, partners were colleagues from Australia, Canada, Netherlands, Norway, Great Britain and the USA. The concept of evidence-based research was officially recognized in 2018 and financed in 2018–2022 with the support of the European Cooperation in Science and Technology of Horizon 2020 EU program. The program brought together subjects (universities) from over than 40 countries of the world.

In 2019, the Kazan State Medical University was included into the program as an observer. The program was extended until 2023 because of the pandemic.

The COVID-19 pandemic exacerbated the problem of waste in research; infodemic developed in research practice. Thus, about 11 and over 65 systematic reviews per day were published globally in 2010 [29] and in 2019, respectively. As of May 2021, only one database contained about 9,000 generalized evidences related to COVID-19 only. It means that about 21 reviews per day were devoted to the coronavirus infection since the WHO had announced the pandemic [29].

Nevertheless, as emphasized in a paper in the *Nature*, fundamental principles of evidence-based medicine should be immutable, whereas its principles, processes and methods should be developed under novel conditions. When the Cochrane Collaboration was founded in the last century, its founders were well aware that systematic reviews should be subjected to regular update taking into account all last trials: '*But the proposal of Archie Cochrane made 50 years ago stating that decisions should be based on rigorous evidence are currently more important than ever*' [29].

So, modern clinical practice relies upon evidence-based facts and achievements more and more. It increasingly refers to meta-analyses and systematic reviews. Currently, the goal is to keep making progress in the direction without numerous unnecessary, costly and ethically unjustified biomedical experimental and clinical trials, which can mislead a physician. Local ethics committees, editorial boards of biomedical journals, experts of scientific funds that determine research financing should pay attention to that.

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EARLY PHASE CLINICAL RESEARCH AS VIEWED BY HEALTHY VOLUNTEERS

Fitilev SB, Vozzhaev AV, Shkrebniova II, Kliuev DA ✉, Saakova LN

Peoples' Friendship University of Russia (RUDN University), Moscow, Russia

Early phase clinical research is an essential step in the development of novel medicinal products. Its main subjects are healthy volunteers. The research quality and outcomes directly depend on how and among whom healthy volunteers are selected and how well the volunteers follow the requirements. Selection of healthy volunteers for participation in early phase clinical research can be influenced by a number of various factors and ethical problems. Better comprehension of volunteer's expectations, potential fears, limiting factors and motives will promote adherence to respective ethical standards and, as a rule, result in qualitative research practice. In this article, authors have tried to analyze the attitude of healthy volunteers towards various aspects of participation in clinical research using own research experience and available literature data. Surveys of healthy volunteers, individual observations and interviews of researchers with participants represented data to be analyzed. Basic variables of interest included the social and demographic portrait of a healthy volunteer, motivation and barriers to research participation, perception of risks by volunteers and their attitude to adverse events, and financial aspects.

Keywords: early phase clinical research, healthy volunteers, ethics, motivation to participation, payment, perception of risks and benefits, adverse events, 'professional' volunteers

Author contribution: Fitilev SB — development of article concept, analysis of scientific data, article editing; Vozzhaev AV — development of article concept, analysis of scientific data, writing an article; Shkrebniova II — collection of data, analysis of scientific data, writing an article; Kliuev DA — review of the article-related publications, statistical calculations, writing an article; Saakova LN — collection of data, review of the article-related publications.

Compliance with ethical standards: voluntary informed consent was obtained from every participant. Questioning was conducted on a voluntary basis.

✉ **Correspondence should be addressed:** Dmitry A. Kliuev
ul. Miklukho-Maclay, 6, Moscow, 117198, Russia; dmitrijkluev070496@gmail.com

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КЛИНИЧЕСКИЕ ИССЛЕДОВАНИЯ РАННИХ ФАЗ ГЛАЗАМИ ЗДОРОВЫХ ДОБРОВОЛЬЦЕВ

С. Б. Фитилёв, А. В. Возжаев, И. И. Шкребнева, Д. А. Клюев ✉, Л. Н. Саакова

Российский университет дружбы народов (РУДН), Москва, Россия

Клинические исследования ранних фаз являются важнейшим этапом разработки новых лекарственных препаратов. Основные субъекты таких исследований — здоровые добровольцы. Качество проведения и соответственно результаты исследований напрямую зависят от того, как и среди кого осуществляется отбор здоровых добровольцев, насколько добросовестно добровольцы соблюдают предъявляемые к ним требования. Сам процесс отбора здоровых добровольцев для участия в исследованиях ранних фаз может подвергаться влиянию ряда достаточно разнообразных факторов и проблем этического характера. Приобретение лучшего понимания ожиданий добровольцев, их потенциальных страхов, сдерживающих факторов и мотивов позволит обеспечить соблюдение соответствующих этических норм и, как следствие, качественное проведение исследований. В настоящее статье авторы попытались проанализировать отношение здоровых добровольцев к различным аспектам участия в клинических исследованиях, опираясь на собственный исследовательский опыт и данные доступной литературы. Материалами для анализа послужили проведенные опросы здоровых добровольцев, отдельные наблюдения и беседы исследователей с участниками. Основными переменными интереса являлись: социально-демографический портрет здорового добровольца, мотивация и барьеры к участию в исследованиях, восприятие добровольцами рисков и отношение к нежелательным явлениям, финансовые аспекты.

Ключевые слова: клинические исследования ранних фаз, здоровые добровольцы, этика, мотивация к участию, вознаграждение, восприятие риска и выгоды, нежелательные явления, «профессиональные» добровольцы

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Соблюдение этических стандартов: добровольное информированное согласие было получено от каждого участника. Анкетирование проводилось на добровольной основе.

✉ **Для корреспонденции:** Дмитрий Алексеевич Клюев
ул. Миклухо-Маклая, д. 6, г. Москва, 117198, Россия; dmitrijkluev070496@gmail.com

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Ethical aspects of participation of healthy volunteers continue to be a key issue of early phases of clinical research (CR) that can't be solved with standard benefit/risk approaches due to the lack of a suggested therapeutic effect and, as a consequence, social benefit for subjects along with potential health risks of various degrees. In this respect, it is necessary to mention significant efforts and success of the society regarding safety and well-being of subjects of the CR reflected in regulatory documents. All experienced researchers are well aware of these and stick to them in daily routine.

However, a subjective attitude of CR participants to regulatory requirements and their actual performance remains a grey area. Systemic examination of its characteristics is not paid enough attention yet, and such studies are sparse. Dichotomic division of

healthy volunteers into 'good' and 'bad' ones, which is habitual in modern practice, is no longer in line with the latest trends and makes us review this issue in detail. Taking into account the available literature data and own more than 15 years of experience at centers of early phases of CR on the basis of public health institutions, the authors tried to analyze and comprehend the attitude of healthy volunteers to various aspects of participation in CR.

Data to be analyzed involved periodic interrogations with anonymous questionnaires, individual observations and interviews of volunteers by investigators. Basic variables of interest included the social and demographic portrait of phase I research participant, motivation and barriers to research participation, awareness about the trial, subjective assessment of its safety, attitude to adverse events (AE), readiness to report them and financial aspects of participation in CR.

MOTIVATION TO PARTICIPATE IN CR

What is the basic motive that urges people to take part in CR as healthy volunteers? This question has been examined and analyzed by foreign researchers for a long time. It is expected that according to many papers, the majority of volunteers decide to participate because of financial compensation. Many of them are commonly people with low income and low level of education [1,2].

A similar fact was established by Russian authors as well. They state that the main motivating factor of participation in bioequivalence studies among healthy volunteers, especially among men, was financial compensation [3].

After a more in-depth analysis, Indian researchers have found a wide list of factors that influence taking a positive decision about participation in phase I clinical research: 29–38 years, being a male, being married, living in urban slums, big family, low income, lack/low level of education, experience in participation [4]. In another work, composed with support of Pfizer, healthy volunteers from the USA, Belgium and Singapore primarily focused on the amount of payment. No significant association with a social and demographic factor has been detected [5].

The described results increasingly become a subject for discussion by specialists dealing with recruiting ethics of economically disadvantaged volunteers, as low income or unemployment can be the reason for insignificant assessment of all risks by volunteers.

It is true that payment wasn't the principal factor in all trials devoted to examination of volunteers' motivation. Thus, Berg et al. (US) found out that altruism was the basic motive to participate in trials of novel drugs among the majority of participants (72%) [6]. Interest in science and medicine, curiosity, social connections and access to free medical aid are commonly considered as secondary motivators [7], which are widely spread among Chinese healthy volunteers [8]. Moreover, over 80% of participants of Pfizer-supported trial reported competence and friendliness of researchers, contribution to science and aid for future patients as additional factors, which are significant while taking decisions [7].

To make a certain portrait of healthy volunteers visiting our research center, anonymous surveying was performed. The survey consisted of several blocks: social and demographic characteristics (gender, age, education, employment, marital status, number of children), activity of participation in clinical research (employment period, number of trials per year, etc.), motivating factors and barriers while taking a solution about participation in the research, and system of payment *payment.*

The survey involved 83 subjects with 37 females and 46 males. The mean age was 34.8 and 33.4 years respectively. 56.5% had higher education; 53.0% held steady employment; 9.6% were unemployed; 30.1% had a common-law marriage; 80.6% had children. Detailed social and demographic characteristics were described in table.

Speaking about motives of healthy volunteers to participate in research, financial compensation was the principal motive (94.0% of survey participants). Secondary motives involved as follows: being useful for the society (76.8%), free medical examination (64.2%), additional communication and expansion of horizons (55.6%).

In some aspects, the obtained results are concordant with the data from the foreign publications mentioned above, i. e. motivation of our volunteers does not differ from the one of volunteers from other countries.

BARRIERS TO PARTICIPATION IN CR

While taking decisions about participation in clinical research, healthy volunteers can commonly come across barriers which seem important to them. The reasons why people do not want to participate in CR have been studied for over 30 years. Thus, it is believed in some old publications that intervention-based health risks, adverse effects and burden in the form of lost time can be considered as barriers to taking a decision about participation [9–11].

Table. General social and demographic characteristics of survey participants (*n* = 83).

Type of data	Parameter, unit of measurement	Value
Demography	Men,%	44.6
	Women,%	55.4
	Age, M±SD, years	34.01±6.99
Social status	Education,% – Higher – Higher, not completed – Secondary, completed (11 classes) – Secondary, not completed (9 classes)	 56.5 24.1 8.4 10.8
	Married,%	30.1
	Children,% – none – 1 – 2 – 3 and more	 19.4 9.6 10.8 60.2
	Employment,% – Have a permanent job – Unemployed – Self-employed – Freelancer	 53.0 9.6 19.3 18.1

According to the results of more modern trials, risks associated with participation and possible adverse effects of the examined medicine were also taken as more significant barriers that prevailed over such motivation factors as 'aid for future patients' [5]. There are also data stating that volunteers were not ready for a more complex trial [7,12–14], in particular, for the ones that suggested performance of invasive procedures such as bone marrow biopsy and lumbar puncture. Only the minority agreed to change their decision when the amount of compensation is increased [15].

Healthy volunteers were rather ready to take a decision about participation if possible adverse effects included loss of hair, increase of weight, moderate pain within an hour and vomiting during a day. At the same time, such adverse events as one-in-a million chance of death, a small chance of renal failure and effect on consciousness were significant barriers to research participation. Among Chinese volunteers, an unexpected reason for refusal was a possibility to let relatives and friends know about participation in clinical research, and i/v administration of medicine [8].

During the mentioned survey of volunteers from our center, barriers that influenced taking a decision about participation included research schedule (87.7%), adverse effects of the examined medicine (87.3%) and a clinical center where the research is held (68.4%).

Particularly interesting was a response of volunteers regarding such a barrier as a clinical center. It can be supposed that conditions of staying and perhaps attitude to volunteers are quite different in every center, as this factor could be the reason for refusal from participation in CR almost in 70% of volunteers.

RESEARCH BURDEN AS VIEWED BY VOLUNTEERS

As far as the degree of safety for a healthy volunteer goes, protocols of CR can commonly be different from each other and include first-in-human administration of medicines, dose escalation study, finding dose-limiting toxicity, examination of medicines with possible immune-mediated adverse events that occur long-term (8–10 weeks) [16], trials conducted at later stages of drug development process, for instance, to assess effects of food, drug interaction, bioequivalence of medicines and biosimilars.

It has been established in the study by Jill A. et al. that the majority of participants can classify phase I research by a degree of risk (moderate, high or extremely high). However, the majority believes that they are personally protected from harm [17].

We were also interested how the nature of Phase I trial influences the decision of volunteers about participation. It has been found during the survey of 79 subjects that 88.3% of those interviewed paid attention to the nature of the research and its potential harm; it is of no importance for 11.5% of people. Those who responded 'yes' were subdivided into two almost equal groups in terms of gender composition (50.7% of males, 49.3% of females) with the mean age of 34.5±7.1 years. The majority of them had a high level of education (59.4% had a higher education, 21.7% had incomplete higher education, 10.4% had secondary education, 8.7% had incomplete secondary education (9 classes)) and no family (66.7%).

SOURCES OF INFORMATION ABOUT CONDUCTED CR — WHAT INFLUENCES THE CHOICE OF A VOLUNTEER?

It is no secret that healthy volunteers have a social network of their own where they exchange data about regional CR, nature of examined medicines regarding their potential tolerability and adverse events that developed (or not developed) among those who have already participated in hospitalization and have been on outpatient supervision. The information is commonly essential when potential volunteers (including beginners) decide about screening at a respective center.

When healthy volunteers were introduced into the database of our center in 2022, over 90% mentioned social network when answering a standard question about the source of data about our institution and conducted study (until coming across the form of informed consent by those volunteers who have already undergone screening). Others mentioned relatives, family members and friends.

Candidates commonly prefer to participate not in the beginning of the trial but following results of the first hospitalizations. Thus, we have found out an interesting fact indirectly confirming as follows: we analyzed qualitative composition (as related to these parameters) of participants who underwent screening from the first (a half of the set of participants of the entire protocol) and subsequent cohorts during the research of 2022.

39 subjects who visited the center for the first time underwent the screening. 14 subjects (10 women and 4 men with the mean age of 31.9 years) wanted to participate in 2 first cohorts, whereas 21 younger (with the mean age of 26.8 years) women (14 subjects) and men (7 subjects) took part in two subsequent hospitalizations. During the interview prior to signing an informed consent form it has been found out that almost all candidates for participation at the start (13 subjects out of 14) had the experience of participation in CR, knew about inclusion of volunteers from social networks into research, and in 70.9% of cases asked an investigator about potential risks of the examined medicine. 2 participants explained their motivation saying that 'if women are involved, the research can't be harmful' and that 'what safety we are talking about if we are mothers of 2 children and have a mortgage?'.

During the interview with volunteers who wanted to take part in cohorts 3 and 4 it has been found out that in 80.9% of cases they have already been told about good tolerability by previous research participants from social networks, whereas only 47.6% of people asked an investigator about the potential danger of the research. All volunteers also had experience of participating in CR at other centers.

Survey of the last candidates (4 subjects) for hospitalization into small cohort 5 who were first-time visitors of our center is remarkable. They made a conscious decision to participate as their husbands (2 women with experience in taking part in CR having 4 and 3 children respectively) and friends (1 woman with no experience and 1 man with experience in participation in CR having no children) took part at early stages of the research. Only a candidate with no experience in participation in CR was really interested in detailed research procedures and safety of a medicine.

ADVERSE EVENTS AS VIEWED BY VOLUNTEERS

In the light of examination of safety of medicines, another, more significant problem arises. It is about reporting of any symptoms developed among volunteers during phase I research. Meta-analysis of the research has shown that adverse effects represent a common phenomenon in similar trials almost in two-thirds of healthy volunteers; many of AE are moderate and/or disappear rather rapidly [18].

Actual adverse effects of the studied medicine can be distorted when healthy volunteers failed to fulfill their obligations prior to the research [19,20], without reporting the AE. It has also been established that almost 30% of the participants either postponed reporting or totally concealed the AE from the

research personnel [21]. The reasons for concealing information about AE included as follows: volunteers forget/poorly remember their symptoms, have difficulties with verbalization of changes within their body, fear of being excluded from the research if they report the AE [22,23]. Healthy volunteers are commonly difficult to understand whether their decision about termination of participation in the research is an adequate reaction to AE for the purpose of own safety.

The reasons for AE underreporting primarily included the participants who undermined the process of clinical research due to their financial motivation [24–26], as healthy volunteers who registered in clinical research to obtain compensation could hardly report an AE if these can result in early discharge or partial payment only.

Based on experience obtained in our center, we also came across a problem when a volunteer could be excluded from a trial when COVID-19 was reported. This aspect was not mentioned in the informed consent form. Many participants regretted that they were frank about the disease they had. They also said that if the informed consent form contained the condition about non-payment of the remaining part of compensation in case of the disease, they would conceal the fact about the disease or report it during the last visit only.

On the other hand, lack of proportional payment can make participants fabricate or exaggerate the rate of AE to leave the research early with full compensation. This is true for the volunteers who wanted parallel participation in several studies.

VOLUNTEER'S DIARY: SHOULD IT BE FILLED OR NOT?

At our center, 64 participants were interviewed when the diary was issued to detect their attitude to the document. Based on the survey, all volunteers were subdivided into the following groups:

1. Those who won't' fill in the diary (5 subjects).

2. Those who would rather fill in the diary (6 subjects).

3. Those who will definitely fill in the diary (53 subjects).

Two participants from the first group believed that 'the diary was useless paper', three of them said that 'they had never had or could have an AE'.

When participants of the second group were asked in what cases they would still make a record in their diaries, 13 people responded that they would report only those events that were significant in their opinion, whereas 6 of those interviewed provided an unexpected response: 'It depends on a clinical research center. It happens that reporting an AE can make an investigator disappointed as he or she doesn't want to fill it in'.

6 people tried not to make written notes without a preliminary interview with an investigator. One woman who took part in CR multiple times laughingly said that 'she is hardly a writer, so she shouldn't be given a diary'. She meant previous participation in a protocol when she left the following note: 'heel scratching'. She just wanted to reveal all available information for the purpose of scientific research.

Many of those from the third group were aware of their liability towards validity of data about the examined preparation (18 subjects) and fulfillment of labor obligations to the Sponsor (35 subjects).

Interview results of 131 healthy volunteers from the USA described their experience with AE including the reasons why they reported or failed to report symptoms [27]. The interviewers found out that the participants had three basic justifications of their behavior when AE reports were composed: economic, health- and data integrity-oriented. The results of the clinical trial display that behavior of those who reported the results is more complex that it was assumed with the previous portraits of healthy volunteers. In the majority of cases, they are ready to refuse from full compensation if, according to them, reporting their symptoms threatens their own safety or research validity.

PAYMENT FOR PARTICIPATION IN CR

It is already common practice both in our country and abroad that healthy volunteers who participate in early phase clinical research are provided financial compensation. The amount of financial compensation is one of the main objects of ethical expertise in early phase CR. Determining the volume of respective payment that would allow to attract enough participants and be proportionate to the provided load, on the one hand, and avoid excessive effect (pressure) while taking a participation decision, on the other hand, is quite controversial. It is the subject of loud discussions in mainly foreign publications devoted to bioethics or clinical research [28–30].

In Russia, the practice of ethical committees and research centers almost lacks any consistency with regard to this matter. Regulatory recommendations are lacking as well. For instance, recommendations to calculate an amount of compensation considering the research design and scope of procedures, recommendations regarding the procedure for paying payment in case of early termination of participation due to various reasons. In fact, every research center calculates the amount of payment taking into account its own ideas and experience with volunteers.

We witnessed situations when the amount and procedure of payment within the same research in various centers of the same city were significantly different.

Russian investigators of early phase CR are well aware of phase 1-related recommendations of the British guidance [31], when it is established that the amount of compensation should correspond to the duration of stay of a volunteer in early phases, number of visits, and rate of research-associated discomfort. Meanwhile, the amount of payment should not depend on the degree of assumed risk associated with participation in CR. However, the question regarding if all our research centers follow the recommendations remains open.

It is interesting that the available literature contains very little data regarding how volunteers assess the adequacy of payments and what their expectations are based on. American authors suggested that volunteers should independently determine the amount of payment for several hypothetical trials and substantiate the decision. It was found out that apart from logistic aspects and temporary load, volunteers mentioned the degree of risk as a key factor that determines the amount of compensation [32]. We are well aware of recommendations of specialists in ethics as far as the issue goes, as the amount of payment should not depend on risk.

There is little evidence of actual amount of compensation for healthy volunteers. Thus, publication by Fisher JA et al. contains data about payments to healthy volunteers in the USA. Thus, payment per one research amounted from 150 to 13,000 US dollars. Meanwhile, less than 2,000, from 2,000 to 4,000, and over 6,000 US dollars were offered for participation in 22.9%, 42.3% and 14.7% of trials respectively. The median of annual earning among volunteers was 4,200 US dollars [33]. The authors concluded that the funds were not enough for adequate existing to rely upon participation in CR as the principal source of income.

Based on experience of conducted research at our center during the last year, it has been shown that volunteers could earn maximum 160,000 rubles each visiting our center only and

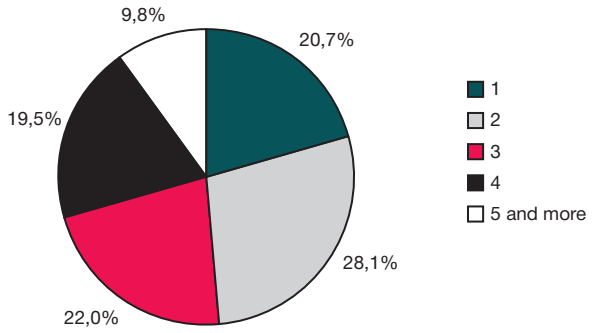

Fig. 1. The structure of replies to the following question 'How many times during a year do you averagely participate in clinical research?'

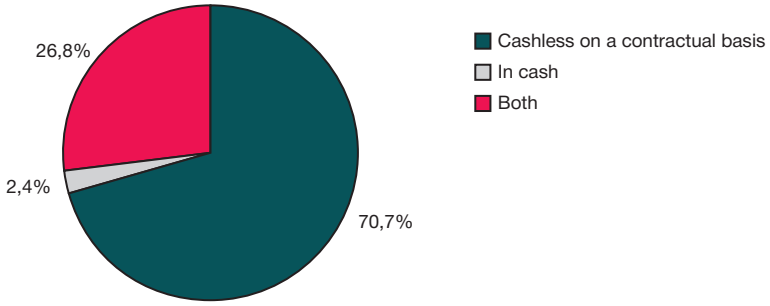

Fig. 2. The structure of replies to the following question 'How do you get your payment?'

observing the recommended timeframes between the trials. It is obvious that the conclusion made was similar to the one of American colleges.

Nevertheless, it is known that some volunteers misuse their participation by referring to (commonly even simultaneously) different early phase centers, trying to earn money with CR only [34] and becoming the so-called 'professional' volunteers. As a rule, the term is used by researchers in negative context.

PROFESSIONAL VOLUNTEERING

In the previous work, we described the over-volunteering and associated risks both for developers of novel medicines, and for volunteers, and ways of struggle with this phenomenon. We were also talking about the measures and procedures used in our research center to detect these cases [35]. Unfortunately, Russian researchers of early phase CR increasingly come across 'professional' volunteers and episodes of misused participation in phase I and bioequivalence CR. Our experience confirms the fact.

28.1% of those interviewed gave 4 and more replies to the following question: 'How many times during a year do you averagely participate in clinical research?' (fig. 1). This raises certain questions because as per recommendations of the Ministry of Health of the Russian Federation [36]*, which are basically followed by all developers while writing CR protocols, the washout period should constitute at least 3 months. In other words, almost one-third of volunteers misuse participation in CR. Men do it more frequently than women (55.4% vs 44.6% respectively, p=0.014).*

The reply to the question 'How do you get your payment*?' was revelation. In accordance with fig. 2, 29.2% of volunteers mentioned that they were* payment *in cash. In this context, conversation with a volunteer, who referred to the Pension Fund upon reaching a certain age to trace tax deductions, was remarkable. He was unpleasantly surprised that in some cases the deductions were absent.*

In our opinion, payment to volunteers should be paid based on the concluded agreement (contract). Apart from the necessity to follow the tax legislation, it can also prevent misuse of participation in CR by volunteers. Contractual relationships emphasize the seriousness and importance of following by volunteers of all requirements and limitations associated with early phase CR.

Thus, efforts to prevent misuse of CR participation by professional volunteers are enough to change the situation in future. We have to state that the problem of over-volunteering has the only effective solution. Unified registries of healthy volunteers (at least at the regional level) have to be created, which was actively reflected in some foreign regulatory documents [31,37]. If the Russian regulatory agency and developers of medicines are not ready to take the initiative as far as the issue goes, the leading (most authoritative) ethical committees and investigators can do it instead. However, the idea can hardly be supported by research subjects presenting a novel view on the problem by healthy volunteers.

CONCLUSION

It is necessary to conclude that the sector of volunteers' participation in early phase CR in Russia is currently in the state of early development. It acquires characteristics, which are inherent to mental features of our population. Tendencies to professionalism are combined with the Russian happy-go-lucky attitude, whereas scrupulous examination of an informed consent form is associated with sympathy towards an investigator and trust in the entire healthcare system. Philosophical perception of life is hardly blended with the common standard operational procedures. This is due to the lack of systemic principles of regulating motivation of CR participants.

There is only one conclusion. As an impossibility to create novel effective medicines without participation of healthy volunteers is an axiom, systemic examination of subjective factors of CR and methods of their influencing constitutes a pressing need of today.

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CARBONIC ANHYDRASE INHIBITORS FOR THE TREATMENT OF GLAUCOMA

Strakhov VV[1], Korsakov MK[2] ✉, Fedorov VN[1,2], Vdovichenko VP[3], Shetnev AA[2], Popova AA[2], Volkhin NN[1,2]

[1] Yaroslavl State Medical University, Yaroslavl, Russia

[2] Ushinsky Yaroslavl State Pedagogical University, Yaroslavl, Russia

[3] Grodno State Medical University, Grodno, Republic of Belarus

Glaucoma is the leading cause of irreversible blindness. Its leading symptom and the most important initial link of the disease pathogenesis is represented by an increase of intraocular pressure (IOP). Decrease of IOP is a basic notion in the therapy of glaucoma. Drug-induced therapy is currently the most widely spread initial intervention to decrease IOP. Prostaglandin analogues are referred to the basic group of pharmacotherapeutic agents, because they are the most effective and well tolerated. Beta-blocking agents are selected as an alternative. Other medicinal products to treat glaucoma include inhibitors of carbonic anhydrase for systemic (acetazolamide and methazolamide) and local (dorzolamide and brinzolamide) use. Systemic inhibitors of carbonic anhydrase are, on the one hand, more active than non-systemic medicinal preparations, and, on the other hand, have numerous side effects which are not safe for humans. Thus, medicinal preparations for local use are most frequently applied in the therapy of glaucoma. If necessary, they are combined with beta-blocking agents or alpha-adrenergic agonists.

Keywords: glaucoma, intraocular pressure, carbonic anhydrase inhibitors

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✉ **Correspondence should be addressed:** Mikhail K. Korsakov
ul. Technoparkovaya, 11/2, Yaroslavl, 150030, Russia; mkkors@mail.ru

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ИНГИБИТОРЫ КАРБОАНГИДРАЗЫ В ТЕРАПИИ ГЛАУКОМЫ

В. В. Страхов[1], М. К. Корсаков[2] ✉, В. Н. Федоров[1,2], В. П. Вдовиченко[3], А. А. Шетнев[2], А. А. Попова[2], Н. Н. Вольхин[1,2]

[1] Ярославский государственный медицинский университет, Ярославль, Россия

[2] Ярославский государственный педагогический университет им. К. Д. Ушинского, Ярославль, Россия

[3] Гродненский государственный медицинский университет, Гродно, Республика Беларусь

Глаукома является ведущей причиной необратимой слепоты. Ее ведущий симптом и важнейшее начальное звено патогенеза заболевания — повышение внутриглазного давления (ВГД), а его снижение — это базисное понятие в терапии глаукомы. Медикаментозная терапия в настоящее время является наиболее распространенным начальным вмешательством для снижения ВГД. Основной группой фармакотерапевтических средств являются аналоги простагландинов, поскольку они наиболее эффективны и хорошо переносятся. В качестве их альтернативы выбираются бета-адреноблокаторы. Ко второму ряду средств для лечения глаукомы относятся ингибиторы карбоангидразы для системного (ацетазоламид и метазоламид) и местного (дорзоламид и бринзоламид) применения. Системные ингибиторы карбоангидразы, с одной стороны, более активны, чем несистемные препараты, а с другой — обладают многочисленными и небезопасными для человека побочными эффектами. Вследствие этого наиболее часто в терапии глаукомы используются препараты для местного применения, которые, при необходимости, комбинируются с бета-адреноблокаторами или альфа-адреномиметиками.

Ключевые слова: глаукома, внутриглазное давление, ингибиторы карбоангидразы

Вклад авторов: В. В. Страхов — разработка концепции и дизайна, редактирование статьи; М. К. Корсаков — ответственность за надлежащее изложение вопросов, связанное с достоверностью данных и целостностью всех частей; В. Н. Федоров — разработка концепции и дизайна, редактирование статьи, ответственность за надлежащее изложение вопросов, связанное с достоверностью данных и целостностью всех частей; В. П. Вдовиченко — сбор, анализ и интерпретация материала, первичное написание; А. А. Шетнев — написание, языковое оформление текста, соответствие научной терминологии; А. А. Попова — оформление списка литературы по порядку упоминания источников в тексте; Н. Н. Вольхин — соблюдение требований оформления статьи для публикации.

✉ **Для корреспонденции:** Михаил Константинович Корсаков
ул. Технопарковая, д. 11/2, г. Ярославль, 150030, Россия; mkkors@mail.ru

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Glaucoma is the leading cause of irreversible blindness [1]. It unites a large group of eye diseases (about 60) with the following features: intraocular pressure (IOP) constantly or periodically exceeds the tolerant (individually tolerant) level; characteristic damage to the optic nerve head and ganglion cells of the retina (glaucoma optic neuropathy — GON), disturbances of visual functions typical of glaucoma are developed.

According to the World Health Organization (WHO), a number of patients with glaucoma around the world varies from 60.5 to 105 mil. people. Meanwhile it is expected that a number of patients will be increased by 10 mil. during the next 10 years. In Russia, over 1 mil. of patients with glaucoma have been revealed. However, a true number of patients is twice as high [Clinical recommendations — Primary open-angle

glaucoma — 2020 (16.02.2021) — Approved by the Ministry of Health of Russia — liter: 22, 98].

Increase of intraocular pressure (IOP) is the leading symptom of glaucoma and the most important initial link of the disease pathogenesis. Recently, the notion of 'tolerant IOP' has become increasingly common. It means the range of IOP, which is safe for this person. Tolerant IOP is not only subject to individual variations, but can also be changed throughout life and under the effect of certain general and eye diseases. Thus, the individual value of tolerant pressure can be significantly lower than the upper limit of statistically normal IOP.

Decrease in intraocular pressure (IOP) is a basic term in glaucoma therapy. In open-angle glaucoma, it is the basis of treatment, in close-angle glaucoma it is a part of complex therapy, which requires a surgery [2–4]. Currently, drug-induced therapy is the most widely spread initial intervention to decrease IOP [2–4]. The basic group of pharmacotherapeutic agents is represented by prostaglandin analogues, as they are the most effective ones (decrease of IOP by 25–33%), well tolerated and they should be instilled into an eye only once a day [2, 3, 5–8]. Ophthalmological forms of beta-blocking agents are selected as an alternative (in case of intolerance or other obstacles for indication of prostaglandins) [2, 3, 8, 9]. They result in IOP decrease by 20–25% [2]. Other agents for glaucoma treatment include carbonic anhydrase inhibitors for systemic (peroral) and local use (decrease of IOP by 20–30%), alpha2-adrenergic agonists, parasympathomimetics, and rho-kinase inhibitors [2, 3, 10, 11].

Ophthalmological agents of carbonic anhydrase inhibitors include dorzolamide (2% eye drops and a combined preparation with 0.5% timolol) and brinzolamide (1% eye suspension and a combined preparation with 0.2% brimonidine) [4]. These agents decrease IOP by 15–20% [2]. Peroral (systemic) carbonic anhydrase inhibitors are more active and represented by acetazolamide (tablets 125 and 250 mg; sustain-action tablets 500 mg) and methazolamide (tablets, 25 and 50 mg). Acetazolamide is used in an acute attack of glaucoma [4]. Today, two generations of drugs from the group of carbonic anhydrase inhibitors are distinguished. The 1st generation carbonic anhydrase inhibitors include acetazolamide and methazolamide, the 2nd generation agents involve non-systemic dorzolamide and brinzolamide.

Comparative effectiveness and tolerance of 1st and 2nd generation carbonic anhydrase inhibitors in glaucoma are reviewed in a number of studies [12–14].

As far as effectiveness of these agents go, it should be noted that acetazolamide produces a more active effect on IOP control as compared with dorzolamide. Thus, in a randomized, double-blind, placebo-controlled study of 40 people at 2 academic sites [12] acetazolamide decreased IOP by 19% in average ($P < 0.001$), whereas dorzolamide did the same by 13% ($P < 0.001$). The result was confirmed during a randomized, multi-centered, double blind, parallel cohort study with 215 patients with open-angle glaucoma or eye hypertension. Dorzolamide (2% solution TID) or acetazolamide (250 mg QID) were added to 0.5 timolol maleate ophthalmic gel-forming solution for 12 weeks [13]. Control of IOP was statistically better ($P = 0.009$) in the group of acetazolamide (0.1 ± 0.42 mm Hg) as compared with dorzolamide (1.9 ± 0.43 mm Hg).

During an earlier study involving 105 patients where acetazolamide and dorzolamide were added to timolol in a randomized fashion while treating glaucoma for 12 weeks [14], similar results were obtained: the average IOP was slightly lower (approximately by 1 mm Hg), during intake of acetazolamide it was reduced in a more active way approximately by 1 mm Hg as compared with dorzolamide [14].

Acetazolamide reduced formation of IOP more actively as compared with dorzolamide: by 30% and 17%, respectively. The difference between the action of acetazolamide and dorzolamide was statistically significant ($P < 0.001$). When acetazolamide was added to dorzolamide, formation of intraocular liquid was additionally reduced by 16% ($P < 0.001$). In case dorzolamide was added to acetazolamide, no additional decrease of the flow was observed ($P = 0.73$) [12]. However, dorzolamide displayed a significantly better tolerance by patients as compared with acetazolamide in all three studies [13, 14].

Acetazolamide was associated with a statistically greater number of systemic adverse events than dorzolamide (dorzolamide 26%, acetazolamide 53%, $p < 0.001$) and cases of treatment discontinuation due to side effects (dorzolamide 2–8%, acetazolamide 24–25%, $p = 0.007$) [13, 14]. In the group of dorzolamide, incidence of systemic adverse reactions was reduced by 50% by week 12 but remained the same in the group of acetazolamide ($p < 0.001$) [14]. A higher rate of adverse events due to administration of acetazolamide 1st generation carbonic anhydrase inhibitors and its more frequent discontinuation were found in these studies as compared with dorzolamide [13, 14].

Thus, as far as 2nd generation agents go, they are safe enough and have obvious advantages in a clinic because they cause adverse effects to a much lesser extent [4]. Regular adverse effects of systemic inhibitors of carbonic anhydrase include paresthesia (of feet and hands), discomfort in the stomach, hypopotassemia, kidney stones and allergic reactions. In case of acetazolamide intake, stomach discomfort and paresthesia occur more frequently than in case of methazolamide [4]. With acetazolamide, very rare, but sometimes severe adverse effects are developed (acute renal insufficiency, paralytic ileus, thrombocytopenia, myopia in the highlands, and Steven-Johnson syndrome) [15–19]. Burning and tingling in the eye and such a systemic adverse effect as metallic taste in the mouth are found while using dorzolamide (more frequently) and brinzolamide (less frequently) [4].

It has become a tradition of therapeutic use of the 2nd generation carbonic anhydrase inhibitors to increase effectiveness of prostaglandins or beta-adrenal blockers. α_2-adrenoceptor agonists are often used for this purpose apart from 2nd generation carbonic anhydrase inhibitors. An extensive meta-analysis (26 tests involving 5583 patients) was conducted to estimate effectiveness and safety of brinzolamide and dorzolamide as add-on therapy to analogs of prostaglandin or beta-blocking agents during treatment of patients with glaucoma or eye hypertension, which can't properly control IOP in monotherapy [20]. It has been shown that brinzolamide and timolol were not significantly different regarding decrease in IOP as addition to prostaglandins; equal effectiveness of administration was found during comparison with dorzolamide.

As compared with brimonidine (BID), brinzolamide caused a more significant decrease in IOP in the morning ($P < 0.0001$), but not during the rest of the day, when its effectiveness was equal to that of brimonidine (BID). When brimonidine was used thrice a day, it provided a greater effect than while taking brinzolamide TID ($P = 0.02$). The study has shown that brinzolamide, dorzolamide and timolol are similarly safe and produce no serious adverse effects.

It has been found out that brinzolamide as addition to prostaglandins or beta-adrenoblockers effectively reduced IOP in patients with refractory glaucoma or eye hypertension without causing significant adverse reactions [20].

In two studies, effectiveness of additional therapy with α_2-adrenomimetics or 2nd generation carbonic anhydrase inhibitors combined with prostaglandin preparations has been compared [21].

163 patients with primary open-angle glaucoma, exfoliative glaucoma or eye hypertension with IOP who obtained travoprost 0.004% participated in the double-blind, three-month, randomized, multi-centered, parallel-group clinical study. The patients were randomized to obtain additional therapy with brimonidine 0.15% BID (N = 79) or brinzolamide 1% BID (N = 84). Three months of combined therapy in the group of travoprost+brimonidine was followed by a significant decrease in the average daily IOP from 21,7 ± 0,33 mm Hg to 18,4 ± 0,33 mm Hg. Decrease of IOP in both groups was significant. The intergroup difference was significant in favor of brinzolamide (P = 0.035). Authors conclude that a combination of travoprost and brinzolamide was therapeutically more effective in respect to IOP decrease as compared with a combination of travoprost and brimonidine [21].

A single-center, blind, parallel-group, randomized controlled clinical study involving 120 patients with open-angle glaucoma or eye hypertension was devoted to comparative effectiveness of brimonidine, dorzolamide and brinzolamide in relation to IOP decrease when used as an add-on therapy to prostaglandin analogues [22].

Bimatoprost, latanoprost or travoprost administered once a day belonged to prostaglandin analogues. The patients were randomized only if add-on therapy was provided: 0.15% of brimonidine tartrate (*n* = 41), 2% dorzolamide hydrochloride (*n* = 40) or 1% of brinzolamide (*n* = 39) were administered TID for 4 months.

RESULTS

The mean value of IOP was compared every hour at baseline in all groups. After initiation of add-on therapy, the mean IOP was significantly decreased in all examined groups of patients. However, add-on therapy was followed by a significant decrease of the mean IOP in all examined groups of patients. During this study, a mean change of IOP from baseline was greater in the group of brimonidine as compared with dorzolamide and brinzolamide (P < 0.001). Effectiveness of dorzolamide and brinzolamide was nearly the same [22].

When an effect of brinzolamide and timolol IOP on therapeutic effectiveness of latanoprost (prospective, randomized study involving 32 patients with primary open-angle glaucoma, normal tension glaucoma or eye hypertension) was compared at 12 weeks, both brinzolamide and timolol reduced IOP by 2.0 mm Hg in average with equal effectiveness (P < 0.01). The medicinal products had equal safety among patients [23].

In another perspective, 8-week, open-label, crossover clinical study (26 patients with glaucoma or eye hypertension) a significantly better therapeutic effectiveness of latanoprost was obtained with add-on of 1% of brinzolamide (TID) or 0.5% of gel-forming solution of timolol (once every morning). However, only add-on therapy with brinzolamide could significantly reduce IOP at night [24].

2nd generation carbonic anhydrase inhibitors are frequently used with adrenergic blocking agents and most frequently timolol. In this case, equal therapeutic effectiveness of brinzolamide and dorzolamide is displayed [25]. 1% brinzolamide was equally effective when administered BID and TID producing an average daily reduction of IOP as compared with baseline within the range of 13.2–21.8% [25]. Thus, a dose given twice a day is one of the least expensive add-ons to therapy with beta-blockers in glaucoma and is associated with lesser direct medical costs as compared with dorzolamide [25].

Another study was related to comparative cost of treatment with brinzolamide and dorzolamide in France, Italy, Portugal and Spain among patients with eye hypertension or primary open-angle glaucoma [26]. The following results were obtained: provided as monotherapy BID or TID, brinzolamide was as effective as dorzolamide TID. Brinsolamide BID and timolol was as effective as a combination of dorzolamide and timilol BID. Direct medical expenses for patients with brinzolamide were lower as compared with those who were administered dorzolamide. The authors concluded that brinzolamide was a more saving alternative to dorzolamide [26].

In 12-month, double-blind, randomized, multi-centered, parallel-group study (34 institutions and 523 patients with open-angle glaucoma or eye hypertension), safety and effectiveness of 2% solution of dorzolamide were compared (TID) with those of 0.5% maleate timolol and 0.5% of betaxolol hydrochloride (BID) [27]. Effect obtained during add-on of dorzolamide to treatment of patients with non-adequate eye hypotensive effectiveness and effect from adding timolol to treatment with dorzolamide were assessed as well.

The following results were obtained during the study: the mean percentage of IOP decrease was obtained at one year of administration of 2% dorzolamide, 0.5% of timolol and 0.5% of betaxolol and amounted to 23%, 25% and 21%, respectively. The authors made a conclusion that an effective decrease of IOP during the course of treatment for up to 1 year when 2% dorzolamide was administered TID was compared with that of 0.5% of betaxolol taken BID [27].

A randomized, open-label, parallel-group study was conducted at 5 sites of Greece to compare a decrease of IOP when dorzolamide was added to timolol [28]. The study included 148 patients with not properly controlled open-angle or pseudoexfoliative glaucoma or eye hypertension resulting in an additive effect of decreased daily IOP from dorzolamide among patents obtaining timolol. At three months, a daily IOP was decreased by 20% in the group of dorzolamide plus timolol. At 3 months, the mean daily decrease of IOP by –4.44 mm Hg (P < 0.001) was estimated with the least square method [28].

Similar results were obtained in a study with 17 patients (timolol plus dorzolamide BID). At three months of treatment, IOP was decreased by 15.6% [29].

A retrospective study of an effect of dorzolamide and brinzolamide on the eye function (mainly field of vision) in open-angle glaucoma and eye hypertension was conducted [30]. No significant protection effect in relation to occurrence of glaucoma in patients with eye hypertension was found during the European Glaucoma Prevention Study where dorzolamide was compared with placebo. In two other long-term studies, superiority of dorzolamide add-on over monotherapy with timolol and superiority of a combination of dorzolamide and timolol over brinzolamide and timolol in relation to ocular blood flow improvement (retrobulbar color Doppler ultrasonography — CDI values) and preservation of the field of vision in patients with glaucoma found 4–5 years ago were reported [30].

Fixed combinations of various agents reducing IOP have acquired important relevance for treatment of open-angle glaucoma. Fixed combinations reduce a number of daily instillations, increasing treatment compliance and reducing an effect of preservatives on the eye [31]. All available publications in relation to fixed combinations of dorzolamide or brinzolamide (in the pharmaceutical market, they are represented by preparations in combination with such a beta-blocker

as timolol) can be conditionally divided into the following groups: 1) studies of effectiveness and side effects of a fixed combination as compared with monotherapy with separate components; 2) comparison of effectiveness and adverse effects of dorzolamide+timolol and brinzolamide+timolol; 3) comparison of dorzolamide+timolol with representatives of other groups (brimonidine+timolol and latanoprost).

Predictably, combinations of dorzolamide/timolol and brimonidine/timolol were more effective than monotherapy with separate components of these combinations [32–37]. Meanwhile, effective decrease of IOP was similar with both combinations [31, 38]. A combination of timolol and brinzolamide was tolerated better than timolol plus dorzolamide due to less eye irritation by brinzolamide [31, 38].

Effectiveness and tolerance of dorzolamide/timolol and brimonidine/timolol were approximately similar. It indirectly testifies to almost equal clinical effectiveness of carbonic anhydrase inhibitors and alpha2-adrenergic agonists [39]. Dorzolamide/timolol is as effective in relation to IOP decrease as latanoprost therapy [40]. Meanwhile, latanoprost was better tolerated by patients. The study confirms validity of clinical recommendations to use prostaglandin preparations in glaucoma as drugs of choice [2, 3].

Pharmaceutical characteristics of combinations are paid attention to as well. Fixed combinations of dorzolamide/timolol with preservative (DTFC) and DTFC without preservatives (PF) were compared [41]. It is found out that PF DTFC has equivalent effectiveness to that of DTFC. Due to improved tolerance and adherence, it has advantages in patients with glaucoma who suffer from ocular surface diseases [41].

CONCLUSION

In treatment of glaucoma, carbonic anhydrase inhibitors have rather high clinical effectiveness in IOP decrease and (mainly, 2nd generation carbonic anhydrase inhibitors) low risk of serious side effects. They can be used as alternative agents when it is impossible to administer drugs of choice such as ophthalmic agents belonging to the group of prostaglandins or beta-blockers. When monotherapy of glaucoma with beta-blocking agents is not effective enough, fixed combinations of brinzolamide or dorzolamide and timolol are applied. Meanwhile, brinzolamide is superior to dorzolamide due to less irritation of the eye and pharmacoeconomic advantages.

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