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SPECIAL ARTICLE

Clinical pharmacology in Russia—historical development and current state

Ksenia Zagorodnikova (Goryachkina) · Aleksandra Burbello · Dmitry Sychev · Maxim Frolov · Vladimir Kukes · Vladimir Petrov

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Abstract Clinical pharmacology in Russia has long history and is currently active, but rather unrecognized internationally. It is governmentally approved as a teaching/scientific specialty since 1983 and as a medical specialty since 1997. Courses of clinical pharmacology are included in the undergraduate curricula in the 5th and/or 6th year of education at all medical schools in the Russian Federation. Postgraduate education includes initial specialization in internal medicine with further residency in clinical pharmacology. Governmental legislation recommends that every healthcare institution has either a department or a single position of clinical pharmacologist. Major routine duties include information about and monitoring of medication use, consultations in difficult clinical situations, pharmacogenetic counseling, therapeutic drug monitoring, pharmacovigilance, and participation in drug and therapeutics (formulary) committees. There are official experts in clinical pharmacology in Russia responsible for coordinating relevant legislative issues. The chief expert clinical pharmacologist represents the discipline directly at the Ministry of Health. Research in clinical pharmacology in Russia is extensive and variable, but only some of it is published internationally. Russia is a participant of international societies of clinical pharmacology and therapeutics and collaboration is actively ongoing. There are still certain problems related to the development of the discipline in Russia—some healthcare institutions do not see the need for clinical pharmacology. However, the number of clinical pharmacologists in Russia is increasing as well as their role in physicians' education, national healthcare, and research.

Keywords Clinical pharmacology · Russia · History · Education · Healthcare · Research

Introduction

Clinical pharmacology is a rapidly developing discipline. Its role has been recently reemphasized in the World Health Organization (WHO) position paper [1] and previously in a report from IUPHAR [2]. The need for qualified clinical pharmacologists is unquestionable in the era of dramatically increasing number of medications, changing life expectancies, disease prevalence, and physicians' behavior, creating new spectra of adverse effects—equally influencing individual lives and countries' economy. New medications and the consequences of their use do not know international borders; therefore, international collaboration may strengthen efforts of individual countries and professional groups in providing rational drug use. Despite the fact that Russia is a member of European professional societies, international collaboration with other countries has been limited, which may partly be due to lack of information. Our current aim is, therefore, to describe the development and current state of clinical pharmacology in Russia.

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K. Zagorodnikova (Goryachkina) (✉) · A. Burbello
North-Western State Medical University, Piskarevsky prospect, 47, Saint-Petersburg, Russia
e-mail: ksenia.zagorodnikova@gmail.com

D. Sychev
Russian Medical Academy of Postgraduate Education, Barrikadnaya str. 2/1, Moscow, Russia

M. Frolov · V. Petrov
Volgograd State Medical University, sq. Pavshih bortsov, 1, Volgograd, Russia

V. Kukes
First Moscow State Medical University, Trubetskaya str. 8/2, Moscow, Russia

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Clinical pharmacology in healthcare

The term "clinical pharmacology" was introduced in Russia in early 1960s by an established professor of internal medicine Boris Votchal (1895–1971). He summarized his practical and scientific experience in a monograph entitled "Assays on clinical pharmacology," which was first published in 1963 [3]. In the monograph, he discussed investigation of individual drug response, connection of experimental research and clinical practice, and adverse drug reactions (ADR). It was a period of the very early growth of clinical pharmacology in the world [4, 5]. Boris Votchal used to visit Germany as a guest researcher before the 2nd World War, and he was familiar with European trends in the development of medicine; in 1958, he arranged the first educational course in clinical pharmacology for physicians in Moscow. It was only in 1997 that clinical pharmacology was governmentally approved as a medical specialty. It was recommended that every hospital has one position of clinical pharmacologist per 150 beds and every ambulatory care center has one position per 500 ambulatory visits. Initial time scheduled for education included 6 years of basic medical studies (medical doctor diploma) followed by 1 or 2 years of internship or residency, later it was transformed to include obligatory internship/residency in internal medicine prior to specialization in clinical pharmacology (Supplementary Figure 1). In the end of their certificate studies, new clinical pharmacologists have to pass exams taken by professors in clinical pharmacology, and only then they are allowed to practice. Short-term educational courses for practicing clinical pharmacologists followed by examinations are repeated every 5 years. Major functions of clinical pharmacologists were described and upgraded in 2003 to meet all the requirements stated in the WHO working group report mentioned above [6] (Table 1), with some distinctions—clinical pharmacologists in most hospitals in Russia became most demanded for their service of bedside advice on rational use of antibiotics and microbial resistance monitoring.

The next governmental order in 2010 called "Order of providing medical help to population in the field of clinical pharmacology" strengthened clinical pharmacologists' clinical relevance and described situations when these specialists were supposed to be needed by other clinicians (Table 1). It was also recommended to establish departments of clinical pharmacology in hospitals with more than 500 beds, while smaller hospitals were supposed to have posts for clinical pharmacologists. The recommended number of positions was upgraded to 1 clinical pharmacologist position for every 250 beds or 500 ambulatory visits. This is the final current state of governmental legislation regarding clinical pharmacology in Russia.

Clinical pharmacology interests on the level of policy makers are safeguarded by chief specialist in clinical pharmacology at the Ministry of Health working under direct guidance of the minister. Chief specialist in clinical pharmacology at the Ministry of Health, as well as chief specialists in other medical areas, is responsible for elaborating strategies of development for the area of his expertise, proposition of changes to existing legislation in order to improve and/or modernize provision of medical help in his area, promoting participation of clinical pharmacologists in discussions of governmental initiatives in healthcare, advising and strengthening legislative basis for the ease of work for clinical pharmacologists in local administrations, healthcare, education, and research institutions. He is supported in his work by the network of regional experts, who may propose initiatives, inform about problems relevant in their regions and, in turn, discuss initiatives from the Ministry of Health and/or other regions. Regional experts are elected from the most active and established people in clinical pharmacology, working in either local administrations, or universities. They are not paid for

Table 1 List of current clinical pharmacology specialists' duties in Russia

Duties of clinical pharmacologists according to the governmental law of 1997	Add-ons according to the governmental law of 2003	Add-ons according to the governmental law of 2010
• Monitoring and advice on pharmacotherapy in clinical departments. • Collection of information on adverse drug reactions. • Consultation of patients in cases of adverse effects of medications or resistance to treatment. • Control of parenteral drug use. • Organization of interdisciplinary discussions on difficult cases of treatment and mistakes in pharmacotherapy. • Development of a hospital formulary list. • Control of/participation in/consultation of participants in clinical trials. • Collection and transfer of information about medications. • Organization of seminars on relevant issues regarding medication rational use/adverse effects/interactions.	• Bedside consultations in cases of genetic differences of response. • Use of second-line antibiotics, anticonvulsants, and intravenous iron preparations. • Therapeutic drug monitoring. • Expertise of 5 % of all case histories for evaluation of drug use patterns and quality. • Evaluation of annual expenditures on medications and percentage of essential medications use.	Bedside consultations in the following cases of: • lack of therapeutic effect, • risk of adverse effects/need of TDM, • medications use in pregnancy and breast-feeding, • co-prescription of 5 and more medications together (check for interactions), • resistance to antibacterial treatment, • medications in renal/hepatic failure, and • suspected genetic variability of drug response.

their expert work; they are never related to any pharmaceutical company and never promote any particular commercial interests, which is a prerequisite of being an expert. Executive part of responsibilities lies on city chief experts in clinical pharmacology working in local committees for healthcare. They are responsible for correct implementation of legislation and provide practical help to clinical pharmacologists in their regions (Supplementary Figure 2).

Clinical pharmacology in education

The very first department of clinical pharmacology was established in Moscow in 1972 by professor of general medicine Vladimir Kukes; in 1976, a similar department was established by a Russian basic pharmacologist Professor Karkishenko in Rostov-on-Don—in the south of Russia, some other departments of general medicine and basic pharmacology formed subdivisions of clinical pharmacology, and some also developed laboratories of pharmacokinetics and pharmacogenetics. In 1983, clinical pharmacology was governmentally approved as an educational and scientific discipline. Departments of clinical pharmacology were then established in many, mostly European and central parts of Russia—Saint-Petersburg, Volgograd, Kazan, Smolensk, Novosibirsk (educational course in clinical pharmacology existed there since 1975), and some other. They were organized by both specialists in basic pharmacology and clinical medicine, forming departments of "basic and clinical pharmacology," "pharmacology and therapeutics," "general medicine and clinical pharmacology," "clinical pharmacology and intensive care," "clinical pharmacology and immunology," etc.

Since that time, clinical pharmacology classes were included into all undergraduate medical curricula. The education program for students until now consists of 48- or 72-h course of lectures and seminars on the 5th or 6th year of medical education. The program was initially based on basic pharmacology, but became much closer to clinical practice and now is being updated in order to leave more space to pharmacokinetics and therapeutic drug monitoring, pharmacogenetics, pharmacovigilance, and drug utilization studies. It uses drug-oriented approach—the model of "essential medicines list" similar to the one described by Orme et al. [7]. Students are supposed to see patients and make their own clinical judgment on real-life or simulated clinical questions concerning pharmacotherapy. In some universities, courses of clinical pharmacology are also arranged for residents and interns of other medical specialties, where trainees can refresh their knowledge in pharmacology and practice skills of rational use of medicines in the areas of their specific practical relevance. Several textbooks in clinical pharmacology are available for students and physicians—both Russian [8–10] and translated versions of international [11–13] editions.

Clinical pharmacology in research

Research in the field of clinical pharmacology in Russia covers different aspects of the discipline. There are 26 Russian peer-reviewed scientific journals publishing original papers and reviews in basic and clinical pharmacology, among which 7 are specialized directly in publishing research in clinical pharmacology and rational drug use, 2 in pharmacoeconomy, 2 in pharmacokinetics, and 1 in pharmacovigilance and drug safety. Six of the journals are indexed in PubMed. Still, there is a lack of Russian papers published in international journals, which leaves a large part of Russian research in clinical pharmacology internationally unrecognized. Some examples of Russian research in pharmacogenetics may still be found in PubMed [14–16].

Development of laboratory services in Russia has been difficult due to lack of resources. Only recently, several governmental initiatives directed towards improvement of medical armamentarium in Russia allowed for better equipment of laboratories of clinical pharmacology. These initiatives include the so-called pharmaceutical clusters implying joint efforts in drug development and investigation of pharmaceutical companies, research and healthcare institutions, universities, etc. These clusters allowed for the development of collaboration between academic clinical pharmacologists and pharmaceutical companies and help to improve capabilities of laboratory-based clinical pharmacology. Still laboratory services are not widely incorporated into clinical routine. Therapeutic drug monitoring and pharmacogenetic analyses are primarily available from commercial laboratories. A study performed in 2011 revealed that not more that 35 % of healthcare professionals are aware of existence of pharmacogenetic testing, 65 % of regional chief experts in clinical pharmacology agreed that healthcare professionals are not informed about pharmacogenetic testing, 57 % mentioned lack of laboratories, 42 % mentioned insufficient financing, and 33 % mentioned lack of qualified personnel [17].

Controlled clinical trials

Clinical pharmacologists in Russia are commonly working in pharmaceutical industry and may participate in creating protocols and monitoring of clinical trials. There are a number of ongoing studies of Russian pharmaceutical products—such as antiviral, neurological, metabolic agents, and vaccines, and much more bioequivalence studies where clinical pharmacologists play an important role. The results are generally published in Russian scientific journals.

Pharmacovigilance and clinical pharmacology

The pharmacovigilance system in Russia was established in 1969 right after the publication of the World Health Assembly resolution 20.51 on initiation of international monitoring of ADRs [18] in a form of ministerial department for registration, classification, and information on ADRs, which was carrying all functions of the Federal Pharmacovigilance Center. Its activities were cut down in 1991, but in 1998 Russia officially joined the WHO program for international drug monitoring, and the first governmental law "on medicines" was released, where the order of investigation of new medicines and the responsibility of all medical professionals to monitor and report adverse drug reactions were stated. All these activities were to a significant extent, promoted by another clinical pharmacologist, Vladimir Lepakhin, who worked as a WHO expert in 1970s and participated in the development of several key documents related to the rational use of medicines, human studies of medicines, etc. Based on his initiative, regional pharmacovigilance centers were established in Russia, and in 2008 these centers were officially recognized as an instrument for national post marketing drug safety monitoring. The system changed significantly after 2011, when the duties were delegated to the federal service for surveillance in healthcare, but still it is a responsibility of clinical pharmacologists in healthcare institutions to investigate suspected ADRs, to provide help in reporting, and to inform physicians about arising drug safety concerns.

Current state

There are around 50 educational centers teaching clinical pharmacology in Russia. According to the 2012 statistical data provided by the chief clinical pharmacologist (personal communication), there were 907 clinical pharmacologists working in practical medicine. This number corresponded to 1 specialist per 7 hospitals in Russia and 6 per 1 million inhabitants, which is in agreement with the estimation of 5 to 10 specialists per million inhabitants provided in the recent questionnaire-based study evaluating current state of clinical pharmacology in Europe [19], but the distribution of specialists is unequal in different parts of Russia (Supplementary Figure 3). Although exact data on the number of specialists in each hospital are not available, there are still hospitals with no position of clinical pharmacologist and hospitals where number of working specialists corresponds to that recommended by the government. The prevailing duties of clinical pharmacologists in real-life vary a lot substantially due to lack of laboratory resources in many regions and the poor understanding of the role of clinical pharmacologists by the administrative workers and other medical specialists. In many regions, clinical pharmacologists do not see patients, but rather participate in the process of purchase of medicines for healthcare institutions and analysis of these expenditures, participate in local drug and therapeutic (formulary) committees, perform retrospective analysis of rationality of drug use based on selected patient case histories. Bedside work is mostly limited to adjustment of antimicrobial therapy. Much less common is responsibility for pharmacogenetic counseling, therapeutic drug monitoring, and pharmacovigilance.

Professional association and collaboration in clinical pharmacology

Russian Society of Clinical Pharmacology and Pharmacotherapy (previously Russian Pharmacology Association—Clinical Pharmacology and Therapeutics Section) is a member of European Association for Clinical Pharmacology and Therapeutics (EACPT) since 1998. The average number of its members in Russia is 100. Professor Kukes was the first delegate from Russia. Former chairmen of EACPT directly supported the development of educational programs in clinical pharmacology in Russia. International collaboration with neighboring countries is maintained through the association of clinical pharmacologists and pharmacists of Commonwealth of Independent States. In 2009, the all-Russian society of clinical pharmacologists was established under the guidance of the chief specialist in clinical pharmacology at the Ministry of Health. It joins all working clinical pharmacologists of Russia in discussions of relevant practical and scientific problems, arrangement of educational courses and annual meetings, exchange of research, and establishment of collaborative projects.

Conclusion

Clinical pharmacology in Russia is actively developing and is intimately integrated into healthcare. There are still many obstacles in its way. Many people receiving a certificate as a clinical pharmacologist do not work in the field, which sometimes comes from lack of understanding of the role of clinical pharmacologists in healthcare institutions. Still, many young people are being trained to become clinical pharmacologists, the number of research projects in the field is growing each year, and hopefully international barriers will be overcome, so that Russian specialists may take an active part in the international development of clinical pharmacology.

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Author contributions Dr. Zagorodnikova drafted the initial manuscript and revised it. Dr. Burbello retrieved historical data presented in the text, supervised, and revised the manuscript. Dr. Sychev collected and provided data on research in clinical pharmacology and revised the manuscript. Dr. Frolov provided information on professional associations and collaboration as well as official statistical figures related to the current state of clinical pharmacology. Dr. Kukes co-supervised and revised all sections of the manuscript, mainly in history and education parts. Dr. Petrov co-supervised the review and contributed to its concept.

Ethical considerations The manuscript does not contain clinical studies or patient data.

Conflict of interest The authors declare that they have no conflict of interest.

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