RESEARCH ARTICLE

ISSN 2307-9266 e-ISSN 2413-2241

Scientific and Practical Journal
PHARMACY & PHARMACOLOGY

COMPARATIVE REVIEW OF METHODOLOGIES FOR ESTIMATING THE COST OF ADVERSE DRUG REACTIONS IN THE RUSSIAN FEDERATION AND BRAZIL

G.I. Syraeva[1,2], A.S. Kolbin[1,3], A.V. Matveev[4,5], V.S Panezhina[2]

[1] First St. Petersburg State Medical University named after academician I.P. Pavlov
6–8, Lev Tolstoy St., St. Petersburg, Russia, 197022
[2] Research Center "Eco-safety"
65, Yuri Gagarin Ave., St. Petersburg, Russia, 196143
[3] Medical Academy named after S.I. Georgievsky (structural unit)
of "Crimean Federal University named after S.I. Vernadsky"
5/7, Lenin Bul., Simferopol, Republic of Crimea, Russia, 295007
[4] Russian Medical Academy of Continuing Professional Education (RMA CPE)
Bld. 1, 2/1, Barrikadnaya St., Moscow, Russia, 125993

E-mail: syraevagulnara@gmail.com

Received 28 May 2020 Accepted 25 Oct 2020

The aim of the review article was to highlight the methodologies for assessing the financial costs of adverse drug reactions exemplified by the Russian Federation and Brazil.
Materials and methods: for a comparative analysis, materials from open sources were used. The study of the experience of methods used for assessing the burden of adverse drug reactions, was carried out using the system for calculating payments for medical care by clinical-statistical and clinical-profile groups, the methodology for assessing the severity of adverse events of the US National Cancer Institute, drug-associated problems, and "the decision tree" model.
Results. When comparing the costs of ADR management in the Russian Federation and Brazil, the following results have been obtained: in the Russian Federation, the "cost" of reaction can be estimated only for a limited number of nosological groups that are regulated by the classification of diseases by clinical and statistical groups; in Brazil, when predicting the costs of adverse reactions management, the combination of "the decision tree" method and the Delphi method is used. In the Russian Federation, the cost of the 3rd and above severity adverse event (according to CTCAE v. 4.03), varies from 26,849.22 up to 26,196.37 RUB in the North-West region (St. Petersburg). In Brazil, the cost of ADR ranges from 13 USD (the best scenario for the patient) to 574 USD (the worst scenario for the patient), which is about 975 and 43,000 RUB, respectively. The introduction of methods that make it possible to predict the development and potential outcomes of adverse drug reactions, as well as taking into account the experiences of foreign colleagues in their modeling, will reduce economic costs in the Russian Federation at the federal level.
Conclusion: for the economic value analysis and further forecasting, an improvement of existing methodologies is required. The models used in the Russian Federation ("the decision tree", classification of diseases by clinical groups, Markov model) do not take into account the time factor, therefore, when planning the analysis of potential costs for adverse reactions, it is necessary to reinforce the methods with such tools as QALY, YLL, and YLD.
Keywords: adverse drug reactions; pharmacovigilance; pharmacoeconomics; modeling; disease burden
Abbreviations: ADRs – Adverse drug reactions; AIS – Automatic information system; CICU – Critical and intensive care unit; ALV – artificial lung ventilation; ARCADe – Adverse Reactions in Crimea, Autonomic Database; AWF – average weight factor; CPG – Clinical profile group; CSG – Clinical statistic group; DALY – Disability Adjusted Life Year; DRM – Drug-Related Morbidities; DRP – Drug Related Problems; GBD – Global Burden of Disease; GTA – General Tariff Agreement; HLE – Healthy Life Expectancy; ICU – intensive care unit; MedDRA – Medical Dictionary for Drug Regulatory Affairs; MMR – Maternal Mortality Ratio; MS – Medical substance; NMP – New Medical Problem; NPS – National Pharmacovigilance System; PCNE – Pharmaceutical Care Network Europe; PE – Pharmacoeconomics; PSG – The program of state guarantees of free provision of medical care to citizens; QALY – Quality-adjusted life year; SADR – Serious Adverse Drug Reaction; SAR – Serious Adverse Reaction; SGBP – Program of state guarantees for free provision of medical care to citizens; SOFA – Sequential Organ Failure Assessment; SUS – Sistema Unico de Sau; SUSAR – Suspected Unexpected Serious Adverse Reaction; TF – Treatment Failure; UADR – Unexpected Adverse Drug Reaction; UAE – Unexpected adverse events; USD – United States dollar; WACIF – Weighted average cost intensity factor; YLL – Years of Life Lost; YLD – Years Lived with Disability.

For citation: G.I. Syraeva, A.S. Kolbin, A.V. Matveev, V.S Panezhina. Comparative review of methodologies for estimating the cost of adverse drug reactions in the Russian Federation and Brazil. *Pharmacy & Pharmacology*. 2020;8(5):336-344. **DOI:** 10.19163/2307-9266-2020-8-5-336-344

Для цитирования: Г.И. Сыраева, А.С. Колбин, А.В. Матвеев, В.С. Панежина. Сравнительный обзор методологий оценки стоимости нежелательных лекарственных реакций в Российской Федерации и Бразилии. *Фармация и фармакология.* 2020;8(5):336-344. **DOI:** 10.19163/2307-9266-2020-8-5-336-344

Научно-практический журнал
ФАРМАЦИЯ И ФАРМАКОЛОГИЯ

ОРИГИНАЛЬНАЯ СТАТЬЯ

DOI: 10.19163/2307-9266-2020-8-5-336-344

СРАВНИТЕЛЬНЫЙ ОБЗОР МЕТОДОЛОГИЙ ОЦЕНКИ СТОИМОСТИ НЕЖЕЛАТЕЛЬНЫХ ЛЕКАРСТВЕННЫХ РЕАКЦИЙ В РОССИЙСКОЙ ФЕДЕРАЦИИ И БРАЗИЛИИ

Г.И. Сыраева[1,2], А.С. Колбин[1], А.В. Матвеев[3,4], В.С. Панежина[2]

[1] Федеральное государственное бюджетное образовательное учреждение высшего образования «Первый Санкт-Петербургский государственный медицинский университет имени академика И.П. Павлова» Министерства здравоохранения Российской Федерации
197022, Россия, г. Санкт-Петербург, ул. Льва Толстого, 6–8
[2] ООО «НИЦ Эко-безопасность»
196143, Россия, г. Санкт-Петербург, пр. Юрия Гагарина, 65
[3] Медицинская академия им. С.И. Георгиевского (структурное подразделение) Федеральное государственное автономное образовательное учреждение высшего образования «Крымский федеральный университет имени В. И. Вернадского»
295007, Россия, Республика Крым, г. Симферополь, бул. Ленина 5/7
[4] Российская медицинская академия непрерывного профессионального образования «РМАПО»
125993, Россия, г. Москва, ул. Баррикадная, д. 2/1, строение 1

E-mail: syraevagulnara@gmail.com

Получено 28.05.2020 Принята к печати 25.10.2020

Цель работы: рассмотреть методологии оценок финансовых затрат на сопровождение нежелательных лекарственных реакций на примере Российской Федерации и Бразилии.
Материалы и методы: для сравнительного анализа использовались материалы, находящиеся в источниках с открытым доступом. Изучение опыта применения методик по оценке бремени нежелательных лекарственных реакций проводился с использованием системы расчёта оплаты медицинской помощи по клинико-статистическим и клинико-профильным группам, методики оценки тяжести осложнений Национального института рака США, лекарство-ассоциированных проблем и модели «дерева решений».
Результаты: при сравнении затрат на ведение нежелательных реакций в РФ и Бразилии были получены следующие результаты: в РФ оценить «стоимость» реакций можно только для ограниченного числа нозологических групп, которые регламентированы классификацией заболеваний по клинико-статистическим группам; в Бразилии при прогнозировании затрат на ведение нежелательных реакций используется сочетание метода «дерева решений» и метода Дельфи. В РФ стоимость сопровождения реакций третьей степени тяжести по CTCAE v. 4.03 и выше составляет от 26849,22 руб. до 26196,37 руб. для Северо-Западного региона (г. Санкт-Петербург). В Бразилии стоимость сопровождения реакций составляет от 13 долларов США (затраты, при развитии лучшего для пациента сценария) до 574 долларов США (затраты, при развитии худшего для пациента сценария), что составляет около 975 и 43000 рублей, соответственно. Внедрение методик, позволяющих прогнозировать развитие и потенциальные исходы нежелательных реакций, а также учёт опыта зарубежных коллег при их моделировании, позволит снизить экономические затраты в РФ на федеральном уровне.
Заключение: для анализа экономической стоимости и дальнейшего прогнозирования требуется совершенствование существующих методологий. Применяемые в РФ модели («дерево решений», классификации заболеваний по группам, модель Маркова) не учитывают временной фактор, соответственно, при планировании анализа потенциальных затрат на НЛР требуется дополнение методов такими инструментами как QALY, YLL, YLD
Ключевые слова: нежелательные лекарственные реакции; фармаконадзор; фармакоэкономика; моделирование; бремя болезни
Список сокращений: АИС – Автоматизированная информационная система; ГТС – Генеральное тарифное соглашение; КПГ – Клинико-профильная группа; КСГ – Клинико-статистическим группа; ЛП – Лекарственный препарат; ЛС – Лекарственное средство; НЛР – Нежелательная лекарственная реакция; ННР – Непредвиденные нежелательные (лекарственные) реакции; ОРИТ – Отделение реанимации и интенсивной терапии; ПГГ – Программа государственных гарантий бесплатного оказания гражданам медицинской помощи; СКЗ – Средневзвешенный весовой коэффициент затратоемкости; СННР – Серьезные непредвиденные нежелательные (лекарственные) реакции; ФЭК – Фармакоэкономика; DALY – Disability Adjusted Life Year/эквивалент потери 1 года здоровой жизни; DRM – Drug-Related Morbidities/заболевания связанные с приемом лекарственных средств; DRP – Drug Related Problems/проблемы связанные с приемом лекарственных средств; GBD – Global Burden of Disease/глобальное бремя заболевания; HLE – Healthy Life Expectancy/ожидаемая продолжительность здоровой жизни; MedDRA – Medical Dictionary for Drug Regulatory Affairs/Медицинский словарь для регуляторной деятельности; MMR – Maternal Mortality Ratio/коэффициент материнской смертности; NMP – New Medical Problem/новая медицинская проблема; NPS – National Pharmacovigilance System/национальная система фармаконадзора; PCNE – Pharmaceutical Care Network Europe/Европейская сеть фармацевтической опеки; SAR – Serious Adverse Reaction/серьезные нежелательные (лекарственные) реакции; SOFA – Sequential Organ Failure Assessment/шкала оценки органной недостаточности у пациентов, находящихся на интенсивной терапии; SUS – Sistema Unico de Sau/система здравоохранения Бразилии; SUSAR – Serious Unexpected Serious Adverse Reaction/серьёзные непредвиденные нежелательные (лекарственные) реакции; TF – Treatment Failure/неудача лечения; QALY – Quality-adjusted life year/качество жизни с поправкой на год; UADR – Unexpected Adverse Drug Reaction/непредвиденные нежелательные (лекарственные) реакции; USD – United States dollar/доллар США; YLL – Years of Life Lost/потерянные годы жизни; YLD – Years Lived with Disability/годы жизни связанные с инвалидностью.

INTRODUCTION

The costs of drug provision come to the fore when planning the budget of the healthcare system [1]. It is necessary to take into account not only the benefits of prescribed medicinal products but also the potential risks and predictability of adverse drug reactions (ADRs) development. A comprehensive assessment of the risk/benefit ratio during the prescribing of medicinal products (MPs) should include an analysis of clinical efficacy, a safety profile, and potential economic consequences [2]. Methodological approaches to assessing pharmacoeconomic parameters are varying and include the analysis of the databases on known ADRs, and the subsequent draw of conclusions and formulation of recommendations to minimize ADRs costs; high-quality clinical trial data; the results of clinical and economic research as well as a pharmacoeconomic analysis [3].

Adverse drug reactions are harmful and unexpected reactions in response to the use or withdrawal of a medicinal product prescribed in therapeutic doses to a person for prevention, diagnosis, therapy, or changing physiological functions [4]. The aim of continuous ADRs monitoring is not only to identify previously unknown medical effects and potential drug interactions, but also to control the increase in the frequency of occurrence of known ADRs and/or their severity, to identify risk factors and possible mechanisms that cause them, and to spread information required to improve the prescription of drugs [5].

For a comprehensive assessment of an adverse event, in both global and Russian kinds of practice, the presence and/or the absence of seriousness criterion is also taken into account as well as the expectedness of the event. Therefore, reactions can be classified as unexpected adverse reactions (UADRs), Serious Adverse Drug Reactions (SADR), and Suspected Unexpected Serious Adverse Reactions (SUSAR) (Official website of Roszdravnadzor, 2020). The collection of ADRs data in different countries is carried out in a similar manner – notification forms that contain the data that make possible the identification of the patient, a suspected drug, the ADR description, and information about these sources [6].

According to the information from Roszdravnadzor, about 30% of the notification forms it receives, do not contain the minimum required data for a complete analysis [8].

The deviations in the ADR manifestations, are possible due to various characteristics of the population (demographic, genetic, etc.). In addition, they can be explained by the conditions of drug manufacturing and transportation. It does not make it possible to fully extrapolate the available foreign data to the Russian practice, and requires the study of ADRs on the territory of the Russian Federation.

The pharmacovigilance system, which was introduced into routine medical practice at the post-authorization stage of MPs use around the world, makes it possible to accumulate and evaluate the data on ADRs [9]. Working with these resources, is aimed at collecting and analyzing information on adverse events not specified in the instructions for medical use, UADR, SADR and SUSAR, and drug interactions. The collected information is evaluated by experts of regulatory authorities, often with the involvement of other expert organizations. ADRs databases maintained by WHO and national regulatory authorities, accumulate information on the events related to the safety of MPs, for example, Vigibase, Eudravigilance, FAERS, etc. An Automatic Information System (AIS) for the input of ADR information called "FARMAKONADZOR", has been introduced by the Russian Federation [10]. The ARCADe regional database (Adverse Reactions in Crimea, Autonomic Database) has been used since 2009 on the territory of the Republic of Crimea and cumulates the data of spontaneous reports in the region [11]. Brazil has a National Pharmacovigilance System (NPS) of their own, and it operates as a part of the Brazilian National Health Surveillance Agency (ANVISA) [12].

Regardless of the particular type of a local pharmacovigilance system and pharmacovigilance assessment methods, the obtained data make it possible to draw a preliminary conclusion regarding the safety profile and the effectiveness of drugs. However, spontaneous reporting does not take into account the time factor in the ADRs development, and does not make it possible to assess the pharmacoeconomic costs of a separate ADR, including indirect costs, and additionally, it cannot predict further ADRs development.

THE AIM of this review article is to highlight the methodologies for assessing the financial costs of adverse drug reactions exemplified by the Russian Federation and Brazil.

MATERIALS AND METHODS

The costs of ADRs must be taken into consideration in an integrated manner, i.e., with keeping account of a range of other problems associated with ADRs. A number of pharmacoeconomic (PE) methodological approaches can be used. In this case, the main stages of the analysis, can be divided into two large blocks (or directions): pharmacoeconomic and pharmacoarithmetic ones. In the first block, after assessing the economic and clinical components and their synthesis, the sustainability of the results should be assessed, a sensitivity analysis should be carried out, and after these stages, the conclusions are to be drawn and recommendations oriented towards decision-making in the healthcare sector are to be made. In the second block, the economic component (costs of pharmacotherapy) is assessed, and after assessing the sustainability of the results and the sensitivity analysis, the conclusions are drawn. Unlike the first approach, the conclusions are not prioritized in decision-making for the entire system of public healthcare.

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2020-8-5-336-344

Estimating the costs of ADRs obviously requires a more systematic approach, with an assessment of possible outcomes and a detailed patient routing. The route of a patient in PE models can be outlined using either the decision tree model or the Markov model (or a combination of these two methods). All the three approaches have certain advantages and limitations. Thus, the "decision tree" model considers the state of the system (in this case, the patient's condition) at the input and output, and its final state, i.e., the exit from the model is determined by the sum of initially specified events developing sequentially and having a certain degree of occurrence probability. In the final assessment, a number of factors, e.g. temporal, are excluded. Unlike models of the "decision tree" type, which consider the state of the system at the input and output, Markov models (Fig. 1) take into account the probability of the system transition from one state to another during the so-called Markov cycle, i.e. in a given time interval [13, 14].

Fig. 1 shows the graph of the Markov model, possible in our case. Several states of the patient are presented: "Health", "ADR", "Death" and the "Disease" is known, as well as the probabilities of transition from one state to another (Px) during a given time interval. This Markov cycle can be extended by adding additional states. The duration and frequency of cycles depend on a specific clinical situation. Additional factors taken into account in the process of the model building, make possible evaluating predictions more accurately [14].

The models described above were originally developed to predict the outcomes of infectious diseases. Subsequently, these methodologies were successfully applied in PE modeling of various therapeutic and surgical outcomes, as well as in the assessment of the effectiveness of health technologies. Such modeling algorithms, which include findings from existing databases indicating the frequency and quality of outcomes, can be extrapolated to the prediction and course of ADRs.

When assessing the ADR cost, it seems reasonable to use the European DRP PCNE (Drug Related Problems of Pharmaceutical Care Network Europe) system, which makes it possible to systematize the events related to pharmacological safety issues in validated reports. The versions of the PCNE system, are regularly updated through periodic revisions by a working group of experts. The PCNE approach is based on the coding of problems into several categories: problems, causes, interventions, and outcomes, which in turn are divided into subcategories [11, 15, 16]. It is necessary to take into consideration the fact that modeling, aimed specifically at assessing economic costs during the evaluation of the "global burden of disease" (GBD), also requires keeping account of such indicators as the cost/utility ratio, the analysis of the impact on the budget as well as discounting with a planning time horizon of more than one year. When using the time factor, the following indicators can be used: mortality, maternal mortality ratio (MMR), years lived with disability (YLD), years lost for life (YLL), healthy life expectancy (HLE), disability-adjusted life year (DALY), etc. [17].

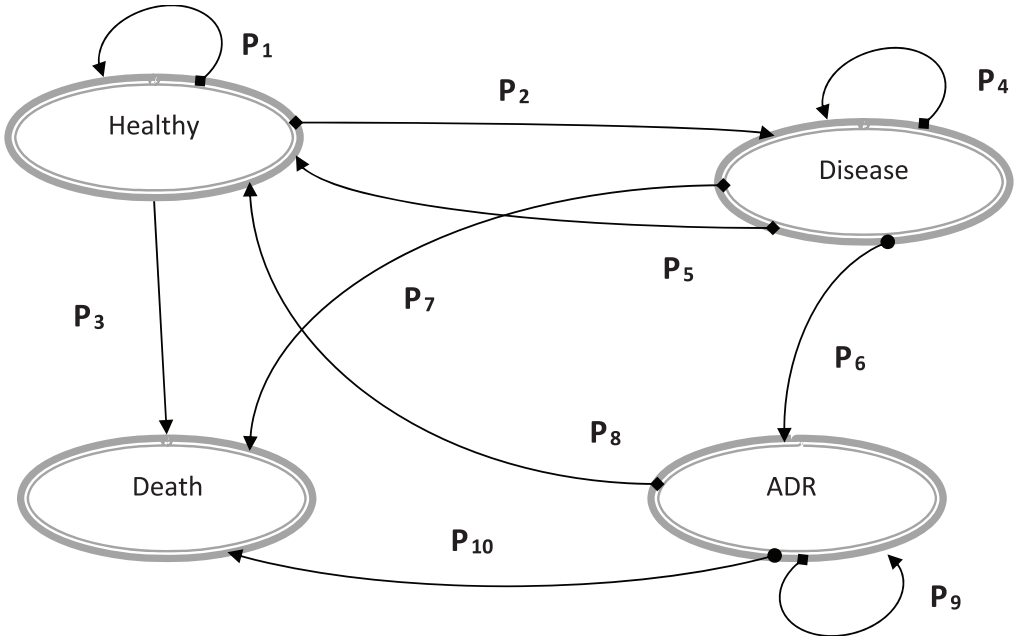

Figure 1 – An example of a possible Markov cycle, where P_x are the probabilities of transition from one condition to another

Table 1 – Cost of adverse drug reactions for 2019, calculated on the basis of the CSG

Adverse events	The cost of drug A therapy, ADR ≥ Stage 3 (roubles)	The cost of drug B therapy, ADR ≥ Stage 3 (roubles)
GTA of Saint-Petersburg	26 849,22	26 196,37
Basic tariff of SGBP	36 790,16	35 593,73
Federal CSG	70 613,19	76 218,45

Note: GTA – General Tariff Agreement; SGBP – Program of state guarantees for free provision of medical care to citizens; CSG – clinical and statistical group; ADR – Adverse Drug Reaction

Table 2 – Results of an expert assessment of ADRs costs in various scenarios according to the data de Feritas [19]

Outcome	Base analysis		Best scenario		Worst scenario	
	Costs (USD)		Costs (USD)		Costs (USD)	
Without additional treatment	Visiting a doctor and primary prescription of drugs	28	Primary prescription of drugs	13	Visiting a doctor and primary prescription of drugs	28
Additional therapy prescribed	Visiting a doctor and primary prescription of drugs + additional therapy prescribed	42	Primary prescription of drugs + additional therapy prescribed	27	Visiting a doctor and primary prescription of drugs + additional medical consultation + additional therapy prescribed	57
Consultation of specialist needed	Visiting a doctor and primary prescription of drugs + additional medical consultation + additional therapy prescribed	71	Visiting a doctor and primary prescription of drugs	28	Special medical consultation and primary prescription of drugs + additional special consultation + additional therapy prescribed	86
Urgent care required	Visiting a doctor and primary prescription of drugs + 2 days of in-hospital treatment	86	Visiting a doctor and primary prescription of drugs + 1 days of ICU treatment	43	Visiting a doctor and primary prescription of drugs + 5 days of in-hospital treatment	173
Hospitalization or prolongation of hospitalization	Visiting a doctor and primary prescription of drugs + 6 days of in-hospital treatment	374	Visiting a doctor and primary prescription of drugs + 3 days of in-hospital treatment	186	Visiting a doctor and primary prescription of drugs + 9 days of in-hospital treatment	574
Long-term follow-up in a medical facility	Visiting a doctor and primary prescription of drugs + 30 days of in-hospital treatment	2715	Visiting a doctor and primary prescription of drugs + 10 days of ICU treatment	1418	Visiting a doctor and primary prescription of drugs + 30 days of ICU treatment	4191
Death	Visiting a doctor and primary prescription of drugs	374	Visiting a doctor and primary prescription of drugs	101	Visiting a doctor and primary prescription of drugs	480

Note: USD – USA dollars; ICU – intensive care unit

As seen from the description of the approaches for collecting information about ADRs, these methodologies do not imply an assessment of the time factor, and therefore, forecasting the ADRs "burden" in the Russian Federation has a number of limitations. Expenditures on diagnostics, treatment, and prolongation of hospitalization, all in relation to a specific nosology, should be taken into account in the assessment of the economic costs of ADRs. In addition, the indirect costs associated with missing working days, disability, and a decrease in the quality of life, should be also taken into consideration.

RESULTS AND DISCUSSION

At the federal level, the Russian Federation maintains a unified safety database. The information is recorded on the basis of Federal Law No. 61-FZ dated 12 April 2010 (as amended on 03.04.2020) "On Circulation of Medicinal Products" and Article 64 "Pharmacovigilance". Since April 2019, coding of ADRs in the Auto-

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2020-8-5-336-344

matic information system of Roszdravnadzor is carrying out using the MedDRA (Medical Dictionary for Drug Regulatory Affairs) classifier with obligatory indicating of the system-organ class of the reaction that has arisen. In addition, the contact person who provided the information, the international non-proprietary name that caused the ADR, its dosage, start and end dates, the causal relationship type for the drug-event pair, the concomitant therapy, de-challenge and re-challenge results for the suspected drug (if applicable), are indicated. According to WHO recommendations, the minimum information to be reported also includes the severity and seriousness of ADR.

Since 2013, the Russian Federation has introduced a system for calculating the reimbursement of medical care from the state foundation of compulsory medical insurance based on diseases classification according to the so-called "Clinical and statistical groups" (CSG). They represent the groups of diseases belonging to the same profile of medical care, and similar in the methods used for diagnosing and treating patients, as well as in average resource intensity (cost, cost structure and set of resources used).

A concept of "clinical profile group" (CPG) which is a group of CSGs and/or individual diseases, united by one profile of medical care", can also be used for such calculations [19]. The group of CPGs includes conditions that require hospitalization. Tariffs to assess the complications of pharmacotherapy, were developed for CPG.

The formation of such groups is carried out on the basis of the parameters that determine the relative capacity of treatment costs: diagnosis, type of health technology or intervention used, patient's age, gender, concomitant pathology or complications of the disease, duration and treatment regimen, duration of staying on artificial lung ventilation (ALV) if necessary. The results of assessing the patient's condition according to clinical scales (for example, the scale for assessing the organ failure in the patients in the intensive care department (Sequential Organ Failure Assessment (SOFA), rehabilitation routing scale, etc.), are also taken into consideration. The average weight factor (AWF) which is calculated according to the given formula and the number of cases in the previous year, are used to calculate the amount of expected similar cases in the next year. The quantity of financial support for a medical organization by each CSG or CPG, is calculated as the sum of the costs of all hospitalizations in a hospital.

According to the data for 2019, Table 1 represents the data on the costs of severity grade 3 ADRs (CTCAE v. 4.03 classification) in medical institutions in St. Petersburg.

It should be notified that in the Russian Federation a unified methodology for assessing the costs of ADRs, has not been developed yet. As a rule, the results of the observational studies and/or database data are analyzed by an expert group, which then interprets the results based on their assessment.

Thus, a standardized approach to assessing pharmacoeconomic costs in connection with the ADRs development in the Russian Federation, has not been developed, either. The existing methodologies are applicable only to a limited number of nosological forms, and only to those events that require hospital observation. Therefore, it is impossible to take into account the time factor and indirect health care costs provoked by ADRs. In addition, extrapolation of results even during hypothetical planning can be difficult due to the fact that different systems for coding clinical manifestations and diseases, are used in pharmacovigilance and pharmacoeconomics (MedDRA and ICD 10).

In the healthcare system of some countries in Latin America, for example, in Brazil (the approach to burden assess in this country is well represented in the literature). A different approach using the DRPs concept (a system that evaluates all medical adverse events caused by ineffective pharmacotherapy and/or non-adherence to recommended treatments) is applied. For example, to assess DRPs, the Brazilian healthcare system SUS (Sistema Unico de Sau) uses a methodology originally developed by Jonson and Butman. It is based on a "decision tree" model representing potential clinical outcomes and direct economic costs. Herewith, direct economic costs also take into account the development of "new diseases" associated with the use of drug therapy (Drug-Related Morbidities; DRM). Costs can be direct, i.e. costs for the ADRs correction, and indirect ones such as lost working days or a period of reduced work ability [19, 20]. The model of ADRs assessment is based on 8 basic characteristics: untreated clinical conditions, inappropriate drug choices, subtherapeutic doses, drug refusals, overdoses, ADRs, drug interactions, and a drug use without appropriate indications. Further modeling involves analyzing the probabilities and costs, associated with the following therapeutic outcomes: 1) no need in additional treatment; 2) additional treatment; 3) visiting a doctor (visiting a medical specialist); 4) emergency department visit with a hospital stay less than 24 hours; 5) hospitalization or hospitalization with a stay in hospital for more than 24 hours; 6) long-term treatment or preliminary hospitalization with a minimum stay of 30 days in hospital or hospitalization to the intensive care unit; 7) death.

Further on, when analyzing an event, the "decision tree" can be represented by several branches. In the first branch of the "optimal outcome," DRMs are divided into three axes of mutually exclusive, sequential negative events: 1) Treatment Failure (TF); 2) New Medical Problem (NMP); 3) a combination of new medical problems and treatment failure (NMP/TF). A New Medical Problem (NMP) represents effects that are superior to those expected after pharmacotherapy (or undesirable effects of pharmacotherapy), including ADRs, dependence, and

overdose. Treatment failure (TF) includes inadequate therapeutic effects arising from inappropriate treatment or dose selection, drug and food interactions, inappropriate drug prescription, medication errors, unnecessary drug use, and inadequate adherence to the drug regimen as well. The second part of the "decision tree" estimates the supposed proportion of DRMs, and the third one consists of clinical negative results from previous DRMs (NMPs, TFs, and NMPs/TFs) [19, 20].

The branches of the tree are mutually exclusive. Therefore, the score should represent the worst scenario for the patient. For example, a patient who is hospitalized due to DRMs has probably already been consulted for treatment adjustments during previous consultations by a healthcare professional. However, this patient should be allocated to those who had been "hospitalized" and should not be taken into account in other branches ("additional treatment" or "visiting–a specialist").

The method has been refined through the involvement of clinical experts using a double-stage Delphi approach. At the first stage, the model can be presented to clinical experts, each of whom assesses the likelihood of the results development described above, in accordance with their own practical and clinical kinds of experience. At the second stage, clinical experts review the predictions of all other participants. If the prognosis of a particular medical expert differs, it explains such a position in order to reach a consensus [21].

An example is the cost estimate of the ADRs, was carried out in one of the hospitals in accordance with the methodology described above by de Freitas et al. [20].

48 medical specialists were recruited as experts. 44 of them were clinical pharmacologists. The results of assessing the ADR costs in the various scenarios, calculated by the authors, are presented in Table 2.

It should be notified that this study is representative of 36% of the Brazilian population [21]. By the group of clinical experts, it was determined that more than half (59%) of patients had DRMs when using at least one drug after a visit to a medical organization/certified physician. The research also shows that the result of an outpatient visit is a prescription for at least one drug. This estimate is consistent with other Brazilian and global data, which indicate that from 50% to 86% of consultations lead to drug prescriptions [22]. Based on the "decision tree" model and the expert review, the average prediction costs of the various ADRs were as follows: NMP, TF, and NMP/TF ratios were 216, 240, and 282 USD, respectively. The results show that among the patients, who received outpatient care and at least one drug, were as follows: 19.5%, 26.8%, and 13% had NMP, TF, and NMP/TF, respectively. These data are comparable to other studies that used the same method (NMP: 10.3%, 28.7%; TF: 16.0%, 23.4%; and NMP/TF: 6.5%, 14. 0%). The cost of medical care for a patient with ADRs was 155 USD. Brazil's average annual costs for ADRs services, range from 9.1 billion USD to 27.2 billion USD (the best and worst-case scenarios, respectively). Of these costs, 3 billion USD will be spent on hospitalization, 10.8 billion USD – on prolongation of hospitalization, which will be the main outcome of ADR. Additional consultations by specialists, as well as the stay of patients in the ICU, will cost 2 billion USD and 900 million USD, respectively [19–21].

The reasons for the aforementioned problems can be explained by failures in treatment monitoring, difficulties with therapeutic adherence, and issues related to the choice or prescription of MPs. According to the experts' estimates, from 53% to 60% of new medical problems (NMPs) and treatment failures (TFs), could have been avoided, in case patients received pharmaceutical care service out of hospital.

The current literature data confirm that ADRs are an urgent problem of modern pharmacoeconomics. Unfortunately, the current pharmacovigilance systems cannot solve a number of problems, such as a low activity of researchers in relation to the ADRs detection, recording, and transmission of information about ADRs, low awareness of the population about the potential risk of ADRs, a low quality of the sent spontaneous reports, etc.

One of the priority-oriented areas of the Russian healthcare system over the past few years has been monitoring the effectiveness, safety, and quality of drugs used at various stages of the clinical and diagnostic process. The experience of the Brazilian drug safety system demonstrates that the introduction of a pharmacologist/clinical pharmacologist consultation prior to prescribing drugs in a specific clinical situation, is cost-effective. Inappropriate prescriptions and lack of patients' follow-up, are the most common causes of ADRs. New diseases and deterioration of existing conditions requiring hospitalization associated with MPs could often be avoided.

Most of ADRs are explained by communication impairments (between patients, caregivers, and healthcare providers), poor adherence to treatment, and lack of knowledge about MPs, their dosages, dosing regimens, and potential drug interactions. The leading task for medical professionals is comprehensive counseling of patients in relation to the prescribed drugs. Sufficient knowledge of health professionals in the field of drug safety will allow them to reduce the frequency of SUSARs, as well as to prevent negative drug-related conditions.

Comprehensive analysis of the information related to drug safety issues, can be an effective economic tool for optimizing costs in the healthcare system. When assessing economic costs, various modeling methodologies or their combinations can be used. However, when predicting, it is important to take into account not only direct and indirect costs but also the ADRs outcomes, which, in turn, can seriously affect a further quality of

ОРИГИНАЛЬНАЯ СТАТЬЯ
DOI: 10.19163/2307-9266-2020-8-5-336-344

life. The methods of the economic assessment of ADRs, are almost not used in Russian practice, with the exception of the cases of the CSG/CPG classification of the diseases, used for the calculation of the reimbursement for medical care from the state foundation of compulsory medical insurance. In general, the number of studies on this issue is limited, and requires active development.

CONCLUSION

The models used in the Russian Federation for the analysis of economic value and further prediction of costs, in contrast to the Brazilian approach, do not take into account the time factor. Respectively, during the planning of the analysis of ADRs potential costs, it is necessary to strengthen the methods with such PE tools as QALY, YLL, YLD, etc.

The introduction of methods for assessing the ADRs economic burden into the Russian routine medical practice, will reduce the direct and indirect costs associated with complications of pharmacotherapy. As shown by the review of Brazilian practice, the analysis of the economic feasibility of prescribing a particular drug should be also subjected to a critical analysis, and the final decision should be made by the teams involving a clinical pharmacologist. This approach will make it possible not only to predict the costs of medical interventions, but also to take into account the potential costs of modifying pharmacotherapy due to the development of ADRs.

FUNDING

This work did not have funding from outside organizations.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

CONTRIBUTION OF AUTHORS

G.I. Syraeva – carrying out a literary search, writing the original text of the article and the resume;
A.S. Kolbin – the formulation of the aim and objectives of the study, text editing;
A.V. Matveev – article editing, preparing the English language text, preparing illustrations;
V.S. Panezhina – carrying out a literary search, preparing the “Materials and Methods” section.

REFERENCES

1. Varpaieva IA, Lapshina SA. Modern trends in differentiated pricing in the pharmacy chain. Financial analytics: problems and solutions. 2014;40:22–34. Russian
2. Engalycheva GN, Syubaev RD, Goryachev DV. Safety Pharmacology Studies of Medicinal Products: Evaluation of Results. The Bulletin of the Scientific Centre for Expert Evaluation of Medicinal Products. 2017;7(2):92–96. DOI: 10.30895/1991-2919-2017-7-2-92-97. Russian
3. Gomon YM, Kolbin AS, Mazurenko SO, Ivanov IG. Principles of clinical and economic analysis of antimicrobial drugs. Kachestvennaya Klinicheskaya Praktika. 2019;2:35–44. DOI: 10.24411/2588-0519-2019-10071. Russian
4. Good vigilance practice of Eurasian economic union. [Access date: 11.09.2020]. Available from: http://www.eurasiancommission.org/ru/act/texnreg/deptexreg/oo/Documents/.
5. Glagolev SV, Gorelov KV, Chizhova DA. Russian pharmacovigilance in a newly regulated environment: two-year results and prospects. Remedium. Journal about the Russian market of medicines and medical equipment. 2019;3:8–14. DOI:10.21518/1561-5936-2019-3-8-14. Russian
6. Association of Clinical Research Organizations. [Access date: 1.01.2020]. Available from: http://acto-russia.org/files/ACTO_open_letter.pdf
7. Shubnikova EV, Darmostukova MA, Bukatina TM, Kaperko DA, Velts NY, Kazakov AS, Snegireva II, Zhuravleva EO, Kutekhova GV. The Adverse Drug Reactions Registered During the Postmarketing Period. Safety and Risk of Pharmacotherapy. 2019;7(1):15–22. DOI:10.30895/2312-7821-2019-7-1-15-22. Russian
8. Hoseva EN, Morozova TE. Problematic aspects of the development of the pharmacovigilance system in the Russian Federation at the present stage (review). Kachestvennaya Klinicheskaya Praktika. 2013;3:40–45. Russian
9. Kolbin A.S. [et al.]. Pharmacovigilance. Moscow: OKI: Buki-Vedi. 2019:248. Russian
10. Federal Service for Surveillance in Healthcare. Electronic services. Automated system Pharmacovigilance. [Access date: 11.09.2020]. Available from: http://www.roszdravnadzor.ru/services/npr_ais
11. Matveev AV, Krasheninnikov AE, Egorova EA, Konyaeva EI. Application of drug-related problems approach to analysis of non-steroidal anti-inflammatory drugs’ safety. Pharmacy & Pharmacology. 2019;7(4):215–223. DOI: 10.19163/2307- 9266-2019-7-4-215-223. Russian
12. The Brazilian Health Surveillance Agency (ANVISA). [Access date: 11.09.2020]. Available from: https://www.who.int/medicines/ areas/quality_safety/regulation_legislation/WA_1.pdf
13. Briggs A, Sculpher M. An introduction to Markov modelling for economic evaluation. Pharmacoeconomics. 1998;13(4):397–409. DOI: 10.2165/00019053-199813040-00003.
14. Kulikov AYu, Nguyen TT, Tikhomirova AV. Modeling methodology in pharmacoeconomics. Pharmacoeconomics. Modern pharmacoeconomics and pharmacoepidemiology. 2011;4:8–15. Russian
15. Eichenberger PM, Lampert ML, Kahmann IV, van Mil JW, Hersberger KE. Classification of drug-related problems with new prescriptions using a modified PCNE classification system. Pharm World Sci. 2010;32(3):362–72. DOI: 10.1007/s11096-010-9377-x.
16. Zimenkovsky AB, Ryvak TB, Khanyk LN. DRP concept as part of the philosophy of rational pharmacotherapy integrated with the pharmaceutical care system. Clinical Pharmacy, Pharmacotherapy and Medical Standardization. 2011;1–2:23–31. Ukrainian
17. The global burden of disease study 2019. The Lancet

Special Issue. [Access date 2020 Sep 11]. Available from: https: // www. thelancet.com/journals/lancet/issue/vol-396no10258/ PIIS0140-6736(20)X0042-0

18. Gomon YM, Kolbin AS, Burbello AT. Pharmacoeconomic aspects of adverse drug reactions. Clinical Pharmacology and Therapy. 2011;1:81–85. Russian
19. de Freitas GRM, Neyeloff JL, Balbinotto Neto G, Heineck I. Drug-Related Morbidity in Brazil: A Cost-of-Illness Model. Value Health Reg Issues. 2018;17:150–157. DOI: 10.1016/j.vhri.2018.07.002.
20. Paula Pereda ACDB, Guidetti B. Economic Burden of Diabetes mellitus in Brazil. Working Papers, Department of Economics of University of São Paulo (FEA-USP). 2019: 32–37.
21. Rocha KSS, Cerqueira Santos S, Boaventura TC, de Araújo DCSA, Silvestre SS, de Lyra Júnior DP. Development and content validation of an instrument to support pharmaceutical counselling for dispensing of prescribed medicines. J Eval Clin Pract. 2020;26:134–141. DOI:10.1111/jep.13102.
22. Martsevich SY, Navasardjan AR, Komkova NA. Off-Label prescribing. possible causes, types and consequences. legal regulation in the Russian Federation. Rational Pharmacotherapy in Cardiology. 2017;13(5):667–673. DOI: 10.20996/181 9-6446-2017-13-5-667-674. Russian

AUTHORS

Gulnara I. Syraeva – clinical pharmacologist, the head of the department of quality control and quality assurance of clinical trials at Scientific Research Center “Eco-Safety” LLC, postgraduate student of the Department of Clinical Pharmacology of First St. Petersburg State Medical University n. a. academician I.P. Pavlov. ORCID ID: 0000-0001-6635-9786. E-mail: syraevagulnara@gmail.com

Aleksey S. Kolbin – Doctor of Sciences (Medicine), Professor, the Head of the Department of Clinical Pharmacology and Evidence-Based Medicine of First St. Petersburg State Medical University n. a. academician I.P. Pavlov; Professor of the Department of Pharmacology, Faculty of Medicine of St. Petersburg State University. ORCID ID: 0000-0002-1919-2909. E-mail: alex.kolbin@mail.ru

Alexander V. Matveev – Candidate of Sciences (Medicine), Associate Professor of the Department of Internal Medicine No. 1 with a course in Clinical Pharmacology of the Medical Academy n.a. S.I. Georgievsky of Crimean Federal University n. a. S.I. Vernadsky; Associate Professor of Clinical Pharmacology and Therapy department of Russian Medical Academy of Continuing Professional Education (RMA CPE). ORCID ID: 0000-0002-6636-3950. E-mail: avmcsmu@gmail.com

Vera S. Panezhina – a general practitioner, a doctor of functional diagnostics at Scientific Research Center “Eco-Safety”. ORCID ID: 0000-0002-5602-5536. E-mail: panezhina.doc@gmail.ru