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GENDER CHARACTERISTICS OF ADVERSE DRUG REACTIONS DEVELOPMENT: EXPERIENCE OF REGIONAL DATABASE ANALYSIS

A.V. Matveev[1,2,3], A.E. Krasheninnikov[1], E.A. Egorova[2], E.I. Konyaeva[2], N.V. Matveeva[2]

[1] National Pharmacovigilance Research Center
Bld. 2/2, Malaya Sukharevskaya Sq., Moscow, Russia, 127051
[2] Medical Academy named after S.I. Georgievsky
of Vernadsky Crimean Federal University
Bld. 7, 5, Lenin Blvd., Simferopol, Republic of Crimea, Russia, 295007
[3] Russian Medical Academy of Continuing Professional Education (RMA CPE)
Bld. 1, 2, Barrikadnaya St., Moscow, Russia, 125993

E-mail: elena212007@rambler.ru

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The aim of the article is the gender characteristics study of the adverse drug reactions (ADRs) development based on the data of the notification forms registered in the regional database ARCADe (Adverse Reactions in Crimea, Autonomic Database), for the period from 2009 to 2018.

Materials and methods. The objects of the study were 6903 notification forms about adverse drug reactions recorded in the regional database called ARCADe (Adverse Reactions in Crimea, Autonomic Database) for the period from 2009 to 2018. The classification of drugs for separate pharmacological groups was carried out using the codes of the Anatomical Therapeutic Chemical (ATC) classification system of the World Health Organization (WHO) medicinal products, the instructions data of the State Registers of medicinal preparations used in the Russian Federation and Ukraine (for the cases registered before the entry of the Republic of Crimea into the Russian Federation).

Results. A general analysis of the number of cases of the adverse drug reactions (ADRs) development in patients of different genders made it possible to determine that 59.9% (4132 notification forms) of ADRs cases were observed in female patients; 37.7% (2602 cases) – in male patients. In 169 cards (2.4%), information about a patient's gender was missing. The groups with the largest number of the registered cases of ADRs were antimicrobial agents for a systemic use (2864 cases, 41.5% of the total number of the ADRs registered cases), the drugs affecting the cardiovascular (811 cases, 11.7%) and nervous (734 cases, 10.6%) systems. In each of the presented groups, the incidence rate of ADRs in female patients exceeded that in men.

Conclusion. The study of the gender characteristics of the pharmacotherapy safety, carried out on the basis of the notification forms of the ADRs data registered in the Republic of Crimea, confirmed a higher likelihood of developing ADRs in female patients. This may be due to the peculiarities of the pharmacokinetics and pharmacodynamics of drugs in the female body, psychological factors, a more frequent use of drugs by this category of people. The implementation of the drug, taking into account specific features of each gender, can lead not only to better treatment outcomes, but also to increased patients' compliance.

Keywords: gender; gender characteristics; adverse reactions; drugs

Abbreviations: ABDs – antibacterial drugs; AH – arterial hypertension; ATE – angiotensine transforming enzyme; ATC-classification system – anatomical therapeutic chemical classification system; CCBAs – calcium channel-blocking agents; CI – confidence interval; MP – medicinal product; NRTI – Nucleoside Reverse Transcriptase Inhibitor; NNRTIs – Non Nucleoside Reverse Transcriptase Inhibitor; ADR – adverse drug reaction; RAAS – renin-angiotensin-aldosterone system; CVS – cardiovascular system.

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ГЕНДЕРНЫЕ ОСОБЕННОСТИ РАЗВИТИЯ НЕЖЕЛАТЕЛЬНЫХ РЕАКЦИЙ ЛЕКАРСТВЕННЫХ ПРЕПАРАТОВ: ОПЫТ АНАЛИЗА РЕГИОНАЛЬНОЙ БАЗЫ ДАННЫХ

А.В. Матвеев[1,2,3], А.Е. Крашенинников[1], Е.А. Егорова[2], Е.И. Коняева[2], Н.В. Матвеева[2]

[1] Автономная некоммерческая организация «Национальный научный центр фармаконадзора»
127051, Россия, г. Москва, Малая Сухаревская пл., д. 2, к. 2
[2] Институт «Медицинская академия имени С.И. Георгиевского»
Федерального государственного автономного образовательного учреждения высшего образования
«Крымский федеральный университет имени В.И. Вернадского»
295051, Россия, г. Симферополь, бул. Ленина, 5/7
[3] Федеральное государственное бюджетное образовательное учреждение
дополнительного профессионального образования
«Российская медицинская академия непрерывного профессионального образования»
125993, Россия, г. Москва, ул. Баррикадная, д. 2/1, стр. 1

E-mail: elena212007@rambler.ru

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Цель. Изучение гендерных особенностей развития нежелательных реакций (НР) на основании данных карт-извещений о НР лекарственных средств, зарегистрированных в региональной базе ARCADe (Adverse Reactions in Crimea, Autonomic Database) за период 2009–2018 гг.

Материалы и методы. Объектами исследования являлись 6903 карты-извещения о НР лекарственных средств, зарегистрированные в региональной базе НР ARCADe (Adverse Reactions in Crimea, Autonomic Database) за период 2009–2018 гг. Проведение классификации ЛС по отдельным фармакологическим группам осуществлялось с использованием кодов Анатомо-терапевтически-химической (АТХ) классификации лекарственных средств Всемирной организации здравоохранения (ВОЗ), данных инструкций Государственных реестров ЛС Российской Федерации и Украины (для случаев, зарегистрированных до вступления Республики Крым в состав Российской Федерации).

Результаты. Общий анализ количества случаев развития НР у пациентов различного пола позволил определить, что в 59,9% (4132 карт-извещений) случаев НР наблюдались у пациентов женского пола; в 37,7% случаев (2602 случая) – у пациентов мужского пола. В 169 картах (2,4%) информация о поле пациента отсутствовала. Группами с наибольшим количеством зарегистрированных случаев НР стали противомикробные средства для системного применения (2864 случая, 41,5% от всего количества зарегистрированных случаев НР); средства, влияющие на сердечно-сосудистую (811 случаев, 11,7%) и нервную (734 случаев, 10,6%) систему. В каждой из представленных групп частота развития НР у пациентов женского пола превышала таковую у мужчин.

Заключение. Изучение половых особенностей безопасности фармакотерапии, проведенное на основании данных карт-извещений о НР ЛС, зарегистрированных в Республике Крым, подтвердило более высокую вероятность развития нежелательных последствий применения ЛС у пациентов женского пола. Это может быть обусловлено особенностями фармакокинетики и фармакодинамики лекарственных препаратов в организме женщины, психологическими факторами, более частым применением ЛС данной категорией лиц. Осуществление выбора лекарственного препарата с учетом специфических для каждого пола особенностей может привести не только к лучшим результатам лечения, но и к повышению комплаентности пациентов.

Ключевые слова: пол; половые особенности; нежелательные реакции; лекарственные средства

Список сокращений: АБП – антибактериальные препараты; АГ – артериальная гипертензия; АПФ – ангиотензинпревращающий фермент; АТХ-классификация – анатомо-терапевтически-химическая классификация; БМКК – блокаторы медленных кальциевых каналов; ДИ – доверительный интервал; ЛС – лекарственное средство; НИОТ – нуклеозидные ингибиторы обратной транскриптазы; ННИОТ – ненуклеозидные ингибиторы обратной транскриптазы; НР – нежелательная реакция; РААС – ренин-ангиотензин-альдостероновая система; ССС – сердечно-сосудистая система.

INTRODUCTION

At the present stage of the healthcare development, when using certain groups of medicinal products (MPs), the study of gender characteristics of the occurrence and course of various diseases, as well as the variability of patients' of different genders' pharmacological response is becoming increasingly important. Over the past 30 years, such gender differences in the majority of cardiovascular diseases, broncho-obstructive diseases and pathologies of the gastrointestinal tract, have already been studied. For example, women are characterized by a smaller size of the heart and coronary vessels, but the stiffness of their vessels is often higher than in men [1]. The changes in the level of female sex hormones

during the menstrual cycle can affect the main parameters of their heart (blood pressure, heart rate, circulating blood volume) [2, 3]. The lipid level of blood plasma in women may also depend on the level of estrogens and gestagens. The development of cardiovascular diseases caused by atherosclerosis is observed in women 7–10 years later than in men [4]. The main pre-condition for the development of arterial hypertension in female patients is the onset of the postmenopausal period, which is accompanied by the development of hormone deficiency, the activation of the sympathoadrenal system, an increase in body mass index and fluid retention in the body. The features of the arterial hypertension (AH) development in women include a more frequent development of isolated systolic AH with a high risk of target organs damage [2].

Gender features of the bronchopulmonary pathology development are primarily due to the anatomical and physiological features of a female respiratory tract structure, which consist in thickening of the bronchi walls of a small caliber and a decrease in the bronchi lumen. Such changes predetermine a significantly higher incidence of chronic obstructive pulmonary diseases in this category of patients, and are, to a great extent, due to circadian changes in the patients' hormonal background of [4].

The differences due to the patients' gender can also significantly change their pharmacological response when the patients are administered with certain groups of drugs, affecting not only the pharmacokinetics, but also the pharmacodynamics of drugs [5, 6]. This is considerably due to the higher body weight of male patients, the large size of their internal organs and the prevailing indicators of blood plasma volume, which can significantly affect the rate of pharmacokinetic processes.

When prescribing drugs, it is also necessary to take into account the lower rate of the evacuation function of the stomach and small intestine, as well as the rate of biochemical processes in female patients [7]. The hormonal characteristics of women lead to the accumulation of their body fat mass, which is accompanied by a decrease in the water content. These factors play an important role in the distribution of lipophilic and hydrophilic drugs. So, lipophilic drugs are distributed in a woman's body much better than hydrophilic ones. A decrease in the synthesis of acid α1-glycoprotein (a protein that forms a bound fraction of drugs with the drugs of a neutral and basic nature), observed in female patients, leads to a significant increase in the free fraction of drugs and the risk of developing ADRs [5, 8, 9].

Sexual characteristics of the metabolism and excretion processes of drugs are primarily due to high rates of activity of the phase II enzymes of metabolism, a glomerular filtration rate and a renal blood flow in male patients. These factors predetermine high rates of the main pharmacokinetic parameters of drug excretion in this category of individuals. The studies have shown that women have a 10–25% lower glomerular filtration rate than men, even after adjusting for a body size. As a result, the clearance and elimination constants of drugs are significantly reduced, which makes this category of patients the most committed to the development of ADRs [10–13].

Thus, the widespread clinical practice of prescribing identical doses of drugs to women and men, does not take into account gender differences in patients' pharmacokinetics and body weight characteristics. This factor creates high risks of overdosing and the development of adverse reactions in female patients and increases the frequency of hospitalizations due to this [14, 15].

THE AIM of the article is a retrospective study of the gender characteristics of the adverse drug reactions development based on the data of the notification forms about ADRs.

MATERIALS AND METHODS

The data on the development of adverse drug reactions for the period from 1 January 2009 to 31 December of 2018, were obtained from a regional electronic database formed on the FileMaker platform and supporting the entry, storage, search and analysis of the data according to user-defined queries. The access to the database is limited (username/password) and was provided by Matveev A.V. and Konyaeva E.I., the developers of the database, the employees of the Department of Basic and Clinical Pharmacology of the Medical Academy named after S.I. Georgievsky of Vernadsky Crimean Federal University.

The database was formed on the basis of medical notification forms about the development of ADRs, containing the following information: a patient's gender and age, a suspected drug, a method of the drug administration, a description of an adverse reaction, an allergy history, and methods for correcting the AR.

The classification of drugs for separate pharmacological groups was carried out using the codes of the Anatomical Therapeutic Chemical (ATC) classification system of the World Health Organization[1] medicinal products. These instructions of the State Registers of Drugs of the Russian Federation[2] and Ukraine[3] (for the cases registered before the entry of the Republic of Crimea into the Russian Federation).

The event rate (share, % of the total number) was determined using the MS Excel 2016 software of the Microsoft Office package. Confidence intervals (95% CI) were calculated using the Klopper-Pearson method (a binominal distribution) or the Fitzpatrick-Scott method (a multinomial distribution) in the CoinMinD module of the R language. The calculation of the χ^2 test and Fisher's

[1] World Health Organization (WHO) Collaborating Centre for Drug Statistics Methodology. ATC/DDD Index 2021. Available from: https://www.whocc.no/atc_ddd_index/.
[2] State Register of Medicines of the Russian Federation. Available from: https://www.grls.rosminzdrav.ru.
[3] State Register of Medicines of Ukraine. Available from: http://www.drlz.com.ua/.

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exact test were performed using the Past 4.06b program (Oyvind Hammer, Norway).

The disadvantage of the study was the lack of information on the number of prescription cases of certain groups of drugs, which prevented us from obtaining the data on the frequency of adverse drug reactions in the population.

RESULTS

In order to study the gender characteristics of the ADRs development during the use of various drugs groups, 6903 notification forms registered for the corresponding period, were selected from the regional database of spontaneous reports. A general analysis of the number of ADRs development cases in patients of different genders, made it possible to determine that in 59.9% cases (95% CI: 58.7–61%; 4132 notification forms), ADRs were observed in female patients, in 37.7% cases (95% CI: 36.5–38.9%; 2602 cases) – in male patients. In 169 forms (95% CI: 1.3–3.6%; 2.4%), the information about the patients' gender was missing.

A further analysis was aimed at studying the gender characteristics of the ADRs development in the application of certain pharmacological drugs groups. In accordance with the ATC-classification system, 14 groups of drugs corresponding to the codes: "A", "B", "C", "D", "G", "H", "J", "L", "M", " N", "P", "R", "S", "V", are distinguished. The distribution of the ADRs development cases by gender in separate drug groups is presented in Table 1.

The groups with the largest number of registered ADRs cases were antimicrobial agents for systemic use (2,864 cases, 41.5% of the total number of registered ADRs cases); the drugs affecting the cardiovascular (811 cases, 11.7%) and nervous (734 cases, 10.6%) systems. In each of the presented groups, the incidence of ADRs in female patients exceeded that in men.

The analysis of differences in the indicators between the groups is presented in Table 2. A significant difference in the drugs of group G (the drugs that affect the genitourinary system and sex hormones) from all other groups, both in pairwise and overall comparisons, is noteworthy. In this group, the number of ADRs in women was 8.6 times higher than that in men.

The analysis of the classification groups represented above, considered in separate pharmacological groups and the gender characteristics of the ADRs development during their use, was of scientific interest. The incidence rate of ADRs in systemic antimicrobials was 41.5% (95% CI: 40.3–42.7%) of the total number of the reported ADRs cases, i.e. of the largest number among all the studied groups. That requires a more detailed study of the characteristics of the ADRs development in using antimicrobial drugs.

In accordance with the ATC classification, group "J" includes 6 main subgroups: antimicrobials; antifungal; antiviral agents; the drugs active against tuberculosis Mycobacteria; vaccines and sera. The incidence rate and distribution of ADRs cases into the above drugs groups by gender are presented in Table 3.

The results of the ADRs cases analysis made it possible to determine that the ADRs development was most often observed when a group of antimicrobial agents (1940 cases) and antiviral drugs (670 cases) for systemic use were administrated. The significance of differences between groups is presented in Table 4.

The distribution analysis of the ADRs cases between separate groups of drugs is of research interest. Thus, among antimicrobial agents for systemic use, the "leaders" in the incidence of the ADRs cases were beta-lactam antibiotics of the cephalosporin group (937 cases), penicillins (358 cases), as well as quinolone derivatives (280 cases) and preparations of the macrolides and lincosamides group (122 case). The distribution of the presented groups by gender characteristics is shown i n Fig. 1.

Among antiviral drugs, the cases of the ADRs development prevailed when combined antiretroviral drugs (266 cases), non-nucleoside reverse transcriptase inhibitors (NNRTIs) (194 cases) and nucleoside reverse transcriptase inhibitors (NRTIs) (91 cases), were prescribed. Rarely, adverse reactions were observed when a group of protease inhibitors (69 cases), which is also used in the treatment of infection caused by the human immunodeficiency virus, was administrated. The gender characteristics study of the ADRs development in the group of antiviral agents revealed that in all these groups, except NNRTIs, the adverse reactions predominated in female patients. In the NNRTIs group, the ratio of the ADRs development cases in male and female patients was 47.9% and 41.7%, respectively. In 20 notification forms, there was no information about the patients' gender.

The next group under study was the drugs that affect the cardiovascular system. Table 5 presents the analysis results of the ADRs reported cases by patients' gender, and Table 6 shows the significance of differences in the subgroups. In terms of the ADRs incidence, the "leading" groups were the drugs that affect the renin-angiotensin-aldosterone (RAAS) system – 37.48% of cases; the drugs for the heart disease treatment – 17.51% of cases; for calcium channel blockers – 12.45%; for peripheral vasodilators – 10.97% of cases.

In almost each of these groups, the number of the ADRs cases registered in female patients prevailed over the number of the ADRs cases observed in men. Among the drugs that affect the RAAS system, the majority of the ADRs cases were due to the use of angiotensin-converting enzyme (ATE) inhibitors – 199 cases. It is worth noting that the ratio of females and males with the reported ADRs cases was 67.3% in this group (134 reports; 95% CI: 60.4–74.3%) and 32.7% (65 notification forms; 95% CI: 25.7–39.6%), respectively, which indicates pronounced features of the ADRs development when this group of drugs is used in patients of different genders.

Table 1 – Distribution of ADRs development cases by gender characteristics in accordance with ATC-classification system of drugs

Group name of drugs in accordance with ATC classification system	Males, absolute number of cases	Females, absolute number of cases	Information about patients' gender is missing	Total number of ADRs development cases	Percentage of ADRs development cases in using certain drug groups
A – Digestive tract and metabolism	171	435	16	622	9.01
B – Hematopoiesis and blood	157	280	11	448	6.49
C – Cardiovascular system	265	542	4	811	11.75
D – Dermatology	47	78	1	126	1.83
G – Genitourinary system and sex hormones	11	95	1	107	1.55
H – Hormones for systemic use (excluding sex hormones and insulins)	11	28	1	40	0.58
J – Antimicrobials for systemic use	1162	1582	120	2864	41.49
L – Anticancer drugs and immunomodulators	53	69	5	127	1.84
M – Musculoskeletal system	180	310	2	492	7.13
N – Nervous system	328	399	7	734	10.63
P – Antiparasitic drugs, insecticides and repellents	15	19	0	34	0.49
R – Respiratory system	112	181	1	294	4.26
S – Preparations for the treatment of sensory processing disorders	34	37	0	71	1,03
V – Other drugs	56	77	0	133	1.93
Total	2,602	4,132	169	6,903	100

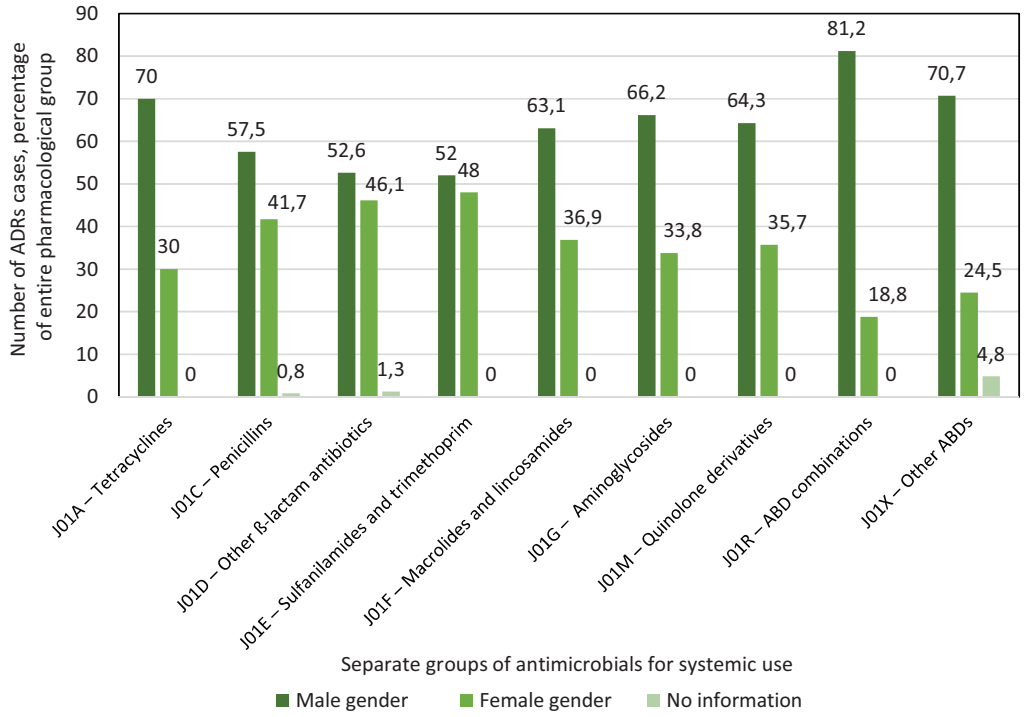

Figure 1 – Distribution of ADRs development cases by gender characteristics in antimicrobial agents group for systemic use (group "J01")

Note: ABDs – Antimicrobial drugs

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Table 2 – Intergroup differences in main ATC groups by gender characteristics

		A	B	C	D	G	H	J	L	M	N	P	R	S	V	All other groups
		X^2 and significance level of criterion														
A – Digestive tract and metabolism			7.015; p=0.03	14.51; p<0.001	5.903; p=0.052	16.345; p<0.001	0.001; p=0.999	45.374; p<0.001	11.669; p=0.003	17.156; p<0.001	45.532; p<0.001	4.937; p=0.085	14.705; p<0.001	13.76; p=0.001	13.546; p<0.001	30.516; p<0.001
B – Hematopoiesis and blood		p=0.029		10.638; p<0.001	1.445; p=0.485	27.254; p<0.001	0.935; p=0.627	9.5541; p=0.008	3.080; p=0.214	7.2823; p=0.026	13.632; p=0.001	1.787; p=0.409	5.391; p=0.067	5.573; p=0.062	5.0142; p=0.081506	1.451; p=0.484
C – Cardiovascular system		p<0.001	p=0.006		1.285; p=0.526	22.673; p<0.001	2.985; p=0.225	50.447; p<0.001	18.863; p<0.001	2.105; p=0.349	25.468; p<0.001	2.046; p=0.359	2.884; p=0.236	6.961; p=0.031	5.0353; p=0.080648	27.95; p<0.001
D – Dermatology		p=0.06	p=0.614	p=0.344		22.616; p<0.001	1.880; p=0.391	4.726; p=0.094146	3.574; p=0.167	0.343; p=0.842	2.478; p=0.29	0.751; p=0.687	0.397; p=0.82	2.547; p=0.28	1.605; p=0.448	1.53; p=0.465
G – Genitourinary system and sex hormones		p<0.001	p<0.001	p<0.001	p<0.001		7.521; p=0.023	47.223; p<0.001	32.882; p<0.001	28.198; p<0.001	46.267; p<0.001	19.793; p<0.001	28.788; p<0.001	32.28; p<0.001	30.651; p<0.001	37.879; p<0.001
H – Hormones for systemic use (excluding sex hormones and insulins)	Fisher's exact test (significance level)	p=1	p=0.54405	p=0.181	p=0.287	p=0.016		3.49; p=0.175	3.069; p=0.216	4.01; p=0.135	5.118; p=0.077	2.871; p=0.238	4.217; p=0.121	5.796; p=0.055	5.761; p=0.056	1.8; p=0.406
J – Antimicrobials for systemic use		p<0.001	p=0.0081787	p<0.001	p=0.081	p<0.001	p=0.186		0.077; p=0.96	22.699; p<0.001	19.806; p<0.001	1.5311; p=0.465	12.631; p=0.002	4.0072; p=0.135	5.808; p=0.055	88.874; p<0.001
L – Anticancer drugs and immunomodulators		p=0.003	p=0.18022	p<0.001	p=0.169	p<0.001	p=0.207	p=0.973		13.078; p=0.001	7.127; p=0.028	1.386; p=0.5	9.132; p=0.01	3.2298; p=0.199	5.385; p=0.0677	2.392; p=0.302
M –Musculoskeletal system		p<0.001	p=0.024	p=0.35	p=0.669	p<0.001	p=0.105	p<0.001	p=0.003		9.677; p=0.008	0.883; p=0.643	0.196; p=0.907	3.569; p=0.168	1.828; p=0.401	10.071; p=0.007
N – Nervous system		p<0.001	p<0.001	p<0.001	p=0.25	p<0.001	p=0.045	p<0.001	p=0.044	p<0.001		0.34; p=0.843	5.078; p=0.079	0.885; p=0.642	1.694; p=0.429	22.297; p<0.001
P – Antiparasitic drugs. insecticides and repellents		p=0.11	p=0.47	p=0.316	p=0.648	p<0.001	p=0.222	p=0.679	p=0.763	p=0.531	p=1		0.562; p=0.755	0.131; p=0.717	0.045; p=0.832	1.301; p=0.522
R – Respiratory system		p<0.001	p=0.06	p=0.22	p=0.796	p<0.001	p=0.117	p<0.001	p=0.013	p=0.869	p=0.076	p=0.622		2.468; p=0.291	1.031; p=0.598	5.7366; p=0.057
S – Preparations for the treatment of sensory processing disorders		p=0.002	p=0.08	p=0.039	p=0.245	p<0.001	p=0.034	p=0.125	p=0.231	p=0.178	p=0.848	p=0.835	p=0.308		0.628; p=0.428	4.453; p=0.108
V – Other drugs		p=0.001	p=0.08	p=0.09	p=0.485	p<0.001	p=0.051	p=0.021	p=0.076	p=0.467	p=0.606	p=0.848	p=0.625	p=0.461		4.108; p=0.128
All other groups		p<0.001	p=0.48	p<0.001	p=0.563	p<0.001	p=0.309	p<0.001	p=0.267	p<0.001	p<0.001	p=0.724	p=0.028	p=0.126	p=0.102	

Table 3 – Distribution of cases of adverse reactions development by gender characteristics in group "J" (antimicrobials for systemic use)

ATC group	Male gender		Female gender		Information about patients' gender is missing		Total number of ADRs development cases	Percentage of total number of ADRs development cases for drugs of group "J" (95% CI)
	Absolute number of cases	% (95% CI)	Absolute number of cases	% (95% CI)	Absolute number of cases	% (95% CI)		
J01 – Antimicrobials for systemic use	800	41,24 (39,0–43,5)	1120	57,73 (55,5–60,0)	20	1,03 (0,0–3,3)	1940	67,74 (65,9–69,6)
J02 – Antifungal drugs for systemic use	11	45,83 (25,8–65,8)	13	54,17 (34,2–74,2)	0	0,0 (0,0–20)	24	0,84 (0–2,7)
J04 – Drugs active against Mycobacteria	85	57,43 (49,4–65,5)	62	41,89 (33,8–49,9)	1	0,68 (0–8,7)	148	5,17 (3,3–7,0)
J05 – Antiviral agents for systemic use	221	32,99 (29,2–36,8)	355	52,99 (49,2–56,8)	94	14,03 (10,2–17,8)	670	23,39 (21,6–25,2)
J06 – Immune sera and immunoglobulins	15	46,88 (29,6–64,2)	17	53,12 (35,8–70,4)	0	0,0 (0,0–17,3)	32	1,12 (0,0–2,9)
J07 – Vaccines	30	60,0 (46,1–73,9)	15	30,0 (16,1–43,9)	5	10,0 (0,0–23,9)	50	1,75 (0,0–3,6)
TOTAL:	1162	40,57 (38,7–42,4)	1582	55,24 (53,4–57,1)	120	4,19 (2,4–6,0)	2864	100

Table 4 – Intergroup differences in ATC subgroups of group "J" by gender characteristics

		J01	J02	J04	J05	J06	J07	All other groups
		X^2 and significance level of criterion						
J01 – Antimicrobials for systemic use	Fisher's exact test (significance level)		0.421; p=0.81	14.777; p<0.001	203.31; p<0.001	0.688; p=0.709	41.899; p<0.001	150.65; p<0.001
J02 – Antifungal drugs for systemic use		p=0.752		1.374; p=0.503	4.517; p=0.104	0.006; p=0.938	5.49; p=0.064	1.1842; p=0.553
J04 – Drugs active against Mycobacteria		p<0.001	p=0.379		40.908; p<0.001	1.5; p=0.472	12.124; p=0.002	20.566; p<0.001
J05 – Antiviral agents for systemic use		p<0.001	p=0.072	p<0.001		6.242; p=0.044	15.073; p<0.001	215.32; p<0.001
J06 – Immune sera and immunoglobulins		p=0.705	p=1	p=0.446	p=0.023		6.486; p=0.039	1.699; p=0.428
J07 – Vaccines		p<0.001	p=0.08	p=0.004	p<0.001	p=0.04		14.702; p<0.001
All other groups		p<0.001	p=0.818	p<0.001	p<0.001	p=0.568	p<0.001	

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Table 5 – Distribution of ADRs development cases by gender characteristics in group "C" (cardiovascular system)

ATC group	Male gender		Female gender		Information about patients' gender is missing		Total number of ADRs development cases	Percentage of total number of ADRs development cases for drugs used in separate groups (95% CI)
	Absolute number of cases	% (95% CI)	Absolute number of cases	% (95% CI)	Absolute number of cases	% (95% CI)		
C01 – Drugs for heart diseases treatment	67	47.18 (39.0–55.4)	71	50.00 (41.8–58.2)	4	2.82 (0.0–11.0)	142	17.51 (14.1–21.0)
C02 – Antihypertensive drugs	0	0.00 (0.0–97.9)	1	100.00 (2.0–197.9)	0	0.00 (0.0–97.9)	1	0.12 (0.0–3.6)
C03 – Diuretics	4	25.00 (0.5–49.5)	12	75.00 (50.5–99.5)	0	0.00 (0.0–24.5)	16	1.97 (0.0–5.4)
C04 – Peripheral vasodilators	29	32.58 (22.2–43.0)	60	67.42 (57.0–77.8)	0	0.00 (0.0–10.4)	89	10.97 (7.5–14.4)
C05 – Angioprotectors	25	36.76 (24.9–48.6)	43	63.24 (51.4–75.1)	0	0.00 (0.0–11.9)	68	8.38 (4.9–11.8)
C07 – Beta–blockers	17	31.48 (18.1–44.8)	37	68.52 (55.2–81.9)	0	0.00 (0.0–13.3)	54	6.66 (3.2–10.1)
C08 – Calcium channel blockers	22	21.78 (12.0–31.5)	79	78.22 (68.5–88.0)	0	0.00 (0.0–9.8)	101	12.45 (9.0–15.9)
C09 – Drugs affecting the RAAS system	91	29.93 (24.3–35.6)	213	70.07 (64.4–75.7)	0	0.00 (0.0–5.6)	304	37.48 (34.0–40.9)
C10 – Antilipedimics	10	27.78 (11.4–44.1)	26	72.22 (55.9–88.6)	0	0.00 (0.0–16.3)	36	4.44 (1.0–7.9)
TOTAL:	265	32.68 (29.2–36.1)	542	66.83 (63.4–70.3)	4	0.49 (0.0–3.9)	811	100

Note: CI – confidence interval; RAAS – renin-angiotensin-aldosterone system.

Table 6 – Intergroup differences in subgroups of group "C" (cardiovascular system) by gender characteristics

		C01	C02	C03	C04	C05	C07	C08	C09	C10	All other groups
		X^2 and significance level of criterion									
C01 – Drugs for heart diseases treatment	Fisher's exact test (significance level)		0.993; p=0.609	3.736; p=0.154	8.239; p=0.016	4.538; p=0.103	6.206; p=0.045	20.855; P<0.001	22.812; P<0.001	6.1166; p=0.047	37.229; p<0.001
C02 – Antihypertensive drugs		p=1		0.327; p=0.567	0.481; p=0.488	0.577; p=0.448	0.456; p=0.5	0.278; p=0.598	0.427; p=0.514	0.381; p=0.537	0.497; p=0.78
C03 – Diuretics		p=0.175	p=1		0.362; p=0.547	0.793; p=0.373	0.247; p=0.619	0.083; p=0.774	0.177; p=0.674	0.043; p=0.835	0.538; p=0.764
C04 – Peripheral vasodilators		p=0.013	p=1	p=0.771		0.299; p=0.585	0.019; p=0.891	2.811; p=0.094	0.228; p=0.633	0.276; p=0.599	0.498; p=0.779
C05 – Angioprotectors		p=0.106	p=1	p=0.56	p=0.614		0.372; p=0.542	4.544; p=0.033	1.21; p=0.272	0.851; p=0.356	0.889; p=0.641
C07 – Beta-blockers		p=0.044	p=1	p=0.761	p=1	p=0.57		1.758; p=0.185	0.052; p=0.819	0.141; p=0.707	0.335; p=0.846
C08 – Calcium channel blockers		P<0.001	p=1	p=0.752	p=0.103	p=0.037	p=0.244		2.5; p=0.114	0.532; p=0.465	6.997; p=0.03
C09 – Drugs affecting the RAAS system		P<0.001	p=1	p=0.785	p=0.695	p=0.311	p=0.872	p=0.125		0.072; p=0.789	4.278; p=0.118
C10 – Antilipedimics		p=0.063	p=1	p=1	p=0.674	p=0.391	p=0.816	p=0.495	p=0.85		0.626; p=0.731
All other groups		P<0.001	p=1	p=0.63	p=1	p=0.648	p=0.91	p=0.027	p=0.12	p=0.657	

Note: RAAS – renin-angiotensin-aldosterone system.

Table 7 – Distribution of cases of adverse reactions development by gender characteristics in group "N" (nervous system)

ATC group	Male gender		Female gender		Information about patients' gender is missing		Total number of ADRs development cases	Percentage of total number of ADRs cases for drugs used in group "N" (95% CI)
	Absolute number of cases	% (95% CI)	Absolute number of cases	% (95% CI)	Absolute number of cases	% (95% CI)		
N01 – Anesthetics	57	40.71 (32.4–49.0)	80	57.14 (48.9–65.4)	3	2.14 (0.0–10.4)	140	19.07 (15.5–22.7)
N02 – Analgesics	99	51.30 (44.2–58.3)	94	48.70 (41.7–55.8)	0	0.00 (0.0–7.1)	193	26.29 (22.7–29.9)
N03 – Antiepileptic drugs	14	31.82 (17.0–46.6)	29	65.91 (51.1–80.7)	1	2.27 (0.0–17.0)	44	5.99 (2.4–9.6)
N04 – Antiparkinsonian drugs	2	50.00 (1.0–98.9)	2	50.00 (1.0–98.9)	0	0.00 (0.0–49.0)	4	0.54 (3.1–4.2)
N05 – Psycholeptics	71	44.65 (36.9–52.4)	88	55.35 (47.6–63.1)	0	0.00 (0.0–7.8)	159	21.66 (18–25.3)
N06 – Psychoanaleptics	53	44.92 (35.9–53.9)	64	54.24 (45.2–63.3)	1	0.85 (0.0–9.9)	118	16.08 (12.5–19.7)
N07 – Other drugs for treatment of nervous system diseases	32	42.11 (30.9–53.3)	42	55.26 (44.0–66.5)	2	2.63 (0.0–13.9)	76	10.35 (6.7–14.0)
TOTAL:	328	44.69 (41.1–48.3)	399	54.36 (50.7–58.0)	7	0.95 (0.0–4.6)	734	100

Note: CI – confidence interval.

Table 8 – Intergroup differences in separate subgroups of group "N" by gender characteristics

		N01	N02	N03	N04	N05	N06	N07	All other groups
		X^2 and significance level of criterion							
N01 – Anesthetics			7.18; p=0.028	1.123; p=0.57	0.202; p=0.904	3.72; p=0.156	1.055; p=0.59	0.105; p=0.949	3.422; p=0.181
N02 – Analgesics	Fisher's exact test (significance level)	0.02		9.281; p=0.01	0.003; p=0.959	1.54; p=0.215	2.69; p=0.261	6.489; p=0.039	6.6; p=0.037
N03 – Antiepileptic drugs		0.559	0.009		0.598; p=0.741	5.637; p=0.06	2.617; p=0.27	1.317; p=0.518	3.737; p=0.154
N04 – Antiparkinsonian drugs		1	1	0.63		0.045; p=0.832	0.069; p=0.967	0.18; p=0.914	0.078; p=0.962
N05 – Psycholeptics		0.183	0.239	0.066	1		1.364; p=0.506	4.26; p=0.119	1.972; p=0.373
N06 – Psychoanaleptics		0.653	0.233	0.212	1	0.651		1.044; p=0.593	1.57; p=0.456
N07 – Other drugs for treatment of nervous system diseases		0.96	0.045	0.545	1	0.174	0.691		2.642; p=0.267
All other groups		0.148	0.042	0.121	1	0.521	0.681	0.239	

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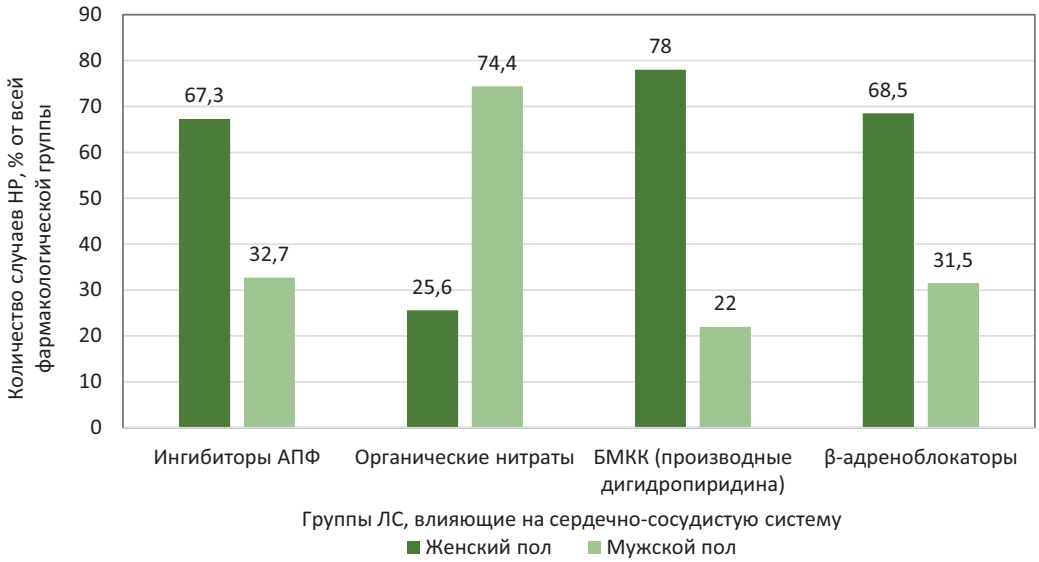

Figure 2 – Distribution of adverse reactions development cases by gender characteristics in the group of drugs that affect cardiovascular system (group "J01")

Note: ADRs – adverse drug reactions; ATE – angiotensine transforming enzyme; CCBAs – calcium channel-blocking agents.

A comparative analysis of differences in the ADRs incidence rate in the administration of combined drugs containing the ATE inhibitors and thiazide diuretics, made it possible to determine that the ratio of the ADRs cases in female and male patients was 75% (95% CI: 62.3–87.7%) (45 cases) and 25% (95% CI: 12.3–37.7%) (15 cases), respectively. Among the drugs for the treatment of heart diseases, the ADRs development cases in the group of organic nitrates prevailed (43 cases). In this pharmacological group, the ADRs cases were more often observed in male patients (32 cases) than in females (11 cases), i.e. in 74.4% (95% CI: 59.5–89.4%) and 25.6% (95% CI: 10.6–40.1%), respectively.

The study of the ADRs caused by the administration of a group of calcium channel-blocking agents (CCBAs), revealed the absolute predominance of the ADRs development cases to dihydropyridine derivatives (100 cases, 99% of the total number of the ADRs to calcium channel-blocking agents, most of which were observed in female patients (78 cases).

In accordance with gender, the ratio of the ADRs development cases in the administration of group "C07" drugs (beta-blockers), was 68.5% (37 cases; 95% CI: 62.9–91.2%) and 31.5% (11 cases; 95% CI: 8.8–37.1%) for female and male patients, respectively.

The distribution of notification forms about ADRs (by gender) of the main pharmacological drugs groups that affect the CVS is shown in Fig. 2.

In terms of the incidence rate of ADRs among the notification forms registered in the ARCADe database, the third place was occupied by the drugs that affect the nervous system functions. A greater number of ADRs in this case was due to the drugs administration of the "N02" group – analgesics (193 cases). It is noteworthy that for the entire group of analgesics, the predominant number of ADRs cases was recorded in men (99 vs 94 cases in women), which distinguishes this group from the rest analyzed.

In 159 cases, the ADRs were associated with the use of the "N05" group – psycholeptics, among which the ADRs development cases in female patients predominated (88 cases). The administration of local anesthetics (group N01) was associated with adverse reactions, 80 of which out of 140 cases, were observed in female patients. The distribution of all undesirable consequences caused by the use of agents that affect the nervous system functions, by gender characteristics, is presented in Table 7.

Among analgesics, the largest number of ADRs was caused by non-narcotic analgesics of the anilide group (93 cases). The distribution of ADRs cases by gender characteristics in the presented group was as follows: in 51 cases, ADRs were observed in male patients, and in 42 cases - in female patients, which amounted to 54.8% (95% CI: 44.7–65, 0%) and 45.2% (95% CI: 35.0–55.3%) of cases, respectively (Table 8).

In the N05 (psycholeptics) group, the majority of ADRs were associated with the use of antipsychotics (126 cases, 79.2% (95% CI: 71.5–87.0%) of the entire N05 group). Butyrophenone derivatives (28 cases) and phenothiazine derivatives with a piperazine structure (23 cases) were the leaders in the incidence rate of ADRs in the group under study. It is important to notify that in the administration of these groups, ADRs were more often observed in the male patients, which was also typical for the entire group of antipsychotic drugs (men – 52.3%, women – 47.7%). For all other groups of drugs that affect the nervous system functions, gender-specific differences were due to the predominance of the ADRs developing risk when they were used in female patients.

DISCUSSION

The results of the present study indicate a higher incidence rate of ADRs in female patients in all groups of drugs, distributed in accordance with the ATC classification system. Taking into account the peculiarities of the pharmacokinetics and pharmacodynamics of drugs in female patients, the data obtained confirm a higher risk of developing the ADRs in this category of individuals [16, 17].

The study of the group of drugs that affect the cardiovascular system functions, revealed a high incidence rate of adverse reactions to the drugs of the ACE inhibitors group in the form of monodrugs and combinations with thiazide diuretics. The data obtained in the study, are comparable with the data presented by Rydberg D.M. et al. [17], in which the ratio of female and male patients with registered ADRs cases to the drugs of the ACE inhibitor group, was 51.6% and 48.4%, respectively, and for the drugs combined with thiazide diuretics – 56.4% and 43.6%, respectively [17]. The data of the literature review studying the features of the ADRs development in patients of different genders administrated with drugs from the ACE inhibitor group, made it possible to identify possible causes of a high incidence rate of ADRs in women. Among them, a more pronounced effect of genetic polymorphisms of bradykinin receptors and ABO genes associated with the level of ATE and the risk of developing cough against the background of the ATE inhibitors use, as well as the effect of changing sex hormones levels during the menstrual cycle on the RAAS system [18]. In experimental models, androgens stimulate the RAAS system, while estrogens and progesterone decrease the plasma renin activity, the ATE activity, and aldosterone levels [19]. There is also evidence of a higher risk of dry cough developing in female patients when using ATE inhibitors, which may be due to the genetic polymorphism of bradykinin receptors and ABO genes associated with plasma ATE levels [20].

The study of gender characteristics of the ADRs development in the administration of

the calcium channel-blocking agents (CCBAs) group (dihydropyridine derivatives), conducted by Rydberg D.M. et al. [17], confirmed the results gained on the predominance of the ADRs development cases in female patients (59% of cases). These data are comparable with the results of studying the safety of amlodipine in clinical practice, which revealed a high risk of developing peripheral edema and a significant effect of this group on the level of blood pressure in females during the use of amlodipine [21].

Similar results on the predominance of the incidence rate of adverse reactions in female patients during the administration of the drugs that affect the cardiovascular system were obtained in the study conducted by the National Pharmacovigilance Center of the Netherlands and the study by Yu Y. et al. [22]. In these studies, the ratio of the ADRs frequency o in female and male patients using antihypertensive drugs was 53.1% and 46.9%, respectively.

Clinical studies have also revealed higher risks of developing ADRs in female patients when using the drugs that affect the central nervous system function (selective serotonin reuptake inhibitors, antidepressants) [23, 24].

The data gained by De Vries et al., which indicate a higher frequency of the ADRs development with the use of tetracycline, penicillin, beta-lactam antibiotics, except for penicillins, macrolides in females [25].

The results of this study concerning the gender characteristics of the ADRs development in the administration of antimicrobials, were comparable with De Vries et al.'s data, which indicate a higher incidence rate of the ADRs development when using tetracycline, beta-lactam antibiotics groups, except penicillins, macrolides in females [25].

CONCLUSION

The study of the gender characteristics of the pharmacotherapy safety, carried out on the basis of the data of the ADRs notification forms registered in the Republic of Crimea, confirmed a higher likelihood of developing undesirable consequences of the drugs in female patients. This may be due to the peculiarities of the pharmacokinetics and pharmacodynamics of drugs in the female body, psychological factors, a more frequent use of drugs by this category of people. However, despite the obvious physical and physiological gender differences, the efficacy and safety features of drugs are very rarely taken into account when conducting pharmacotherapy in females. The implementation of the drug choice, taking into account the specific gender characteristics, can lead not only to better treatment outcomes, but also to the increased patient compliance.

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CONFLICT OF INTERESTS

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTION

Alexander V. Matveev – working out the concept and design of the study, processing the results;
Anatoly E. Krasheninnikov – work out the concept of the study, analysis and interpretation of the results;
Elena A. Egorova – statistical processing of the results, writing the text of the article;
Elena I. Konyaeva – writing the text of the article; Natalia V. Matveeva – analysis of the study results.

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AUTHORS

Alexander V. Matveev – Candidate of Sciences (Medicine), Associate Professor of the Department of Basic and Clinical Pharmacology, Medical Academy named after S.I. Georgievsky of Vernadsky CFU; Executive Director of National Pharmacovigilance Research Center; Associate Professor of the Department of Clinical Pharmacology and Therapy, Head of the Training and Educational Center for Fundamental and Translational Medicine of Russian Medical Academy of Continuing Professional Education (RMA CPE). ORCID ID: 0000-0002-6636-3950. E-mail: avmcsmu@gmail.com

Anatoly E. Krasheninnikov – Doctor of Sciences (Pharmacy), General Director of National Pharmacovigilance Research Center. ORCID ID: 0000-0002-7791-6071. E-mail: anatoly.krasheninnikov@drugsafety.ru

Elena A. Egorova – Candidate of Sciences (Pharmacy), Associate Professor of the Department of Basic and Clinical Pharmacology, Medical Academy named after S.I. Georgievsky of Vernadsky CFU. ORCID ID: 0000-0003-4012-2523. E-mail: elena212007@rambler.ru

Elena I. Konyaeva – Candidate of Sciences (Medicine), Associate Professor of the Department of Basic and Clinical Pharmacology, Medical Academy named after S.I. Georgievsky of Vernadsky CFU. ORCID ID: 0000-0001-5301-8608. E-mail: konyaeva.simferopol@gmail.com

Natalia V. Matveeva – Candidate of Sciences (Medicine), Associate Professor of the Department of Physical Therapy and Sports Medicine, Physiotherapy with the Course of Physical Education, Medical Academy named after S.I. Georgievsky of Vernadsky CFU. ORCID ID: 0000-0002-0119-8106. E-mail: matveevanatasha@gmail.com