REVIEWS

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Review of publications on drug-related problems investigations in osteoporosis patients

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A chronic form of osteoporosis (OP) substantiates a long-term pharmacotherapy of patients, which increases the risk of adverse drug reactions (ADRs) during the therapy. The enhancement of requirements to the quality of safety monitoring carried out in the context of pharmacovigilance and the newly identified safety problems require an improvement of the system of quality control of medicinal products (MPs).

The aim of the work was to review the application of a new promising method for monitoring the drug safety – the system of Drug-Related Problems (DRP) in the osteoporosis pharmacotherapy.

Materials and methods. The following databases and search engines were used to retrieve scientific papers by Russian and foreign authors: PubMed, elibrary.ru, Google Scholar, CyberLeninka, Russian National Library. The information sources were searched using the following keywords and word combinations: “drug-related problems”, “drug safety”, “osteoporosis” (in Russian and English, respectively), as well as the corresponding MeSH terms.

Results. The application of DRP system in the health care of different countries was reviewed, and the risk factors of the problems associated with the use of MPs, the appropriate interventions in case of the detection of high DRP values were investigated. The study of the problems associated with the use of MPs for the treatment of OP during the complex pharmacotherapy made it possible to determine the feasibility of using this method to improve the safety and effectiveness of this kind of treatment in patients.

Conclusion. The analysis of emerging DRPs makes it possible to increase patients’ adherence to the treatment and stop the ADRs. This improves the quality of life of patients and increases the effectiveness of pharmacotherapy. The introduction of such a method of the drug safety research into the system of pharmacovigilance of the Russian Federation is an important step in the development of personalized medicine. A further study of problems associated with the use of drugs in OP patients will also help to reduce the risks arising during the combination pharmacotherapy.

Keywords: drug-related problems; osteoporosis; adverse reactions; pharmacovigilance

Abbreviations: ADR – adverse drug reaction; MP – medicinal product; OP – osteoporosis; DRP – drug-related problems; PCNE – Pharmaceutical Care Network Europe.

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Обзор опыта использования системы проблем, связанных с применением лекарственных препаратов, на примере фармакотерапии остеопороза

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Хронический характер остеопороза (ОП) обосновывает проведение длительной фармакотерапии пациентов, что увеличивает вероятность возникновения нежелательных реакций (НР) при применении лекарственных препаратов (ЛП). Повышение требований к качеству проводимого мониторинга безопасности в рамках осуществления фармаконадзора и выявленные проблемы требуют совершенствования системы контроля качества ЛП.

Цель. Обзор применения перспективного метода мониторинга безопасности ЛП – системы проблем, связанных с применением ЛП (drug-related problems, DRP), при проведении фармакотерапии ОП.

Материалы и методы. Для поиска научных работ российских и зарубежных авторов были использованы следующие базы данных и поисковые системы: PubMed, elibrary.ru, Google Scholar, КиберЛенинка, Российская национальная библиотека. Поиск источников информации осуществляли по следующим ключевым словам и словосочетаниям: «drug-related problems», «проблемы, связанные с применением ЛП», «безопасность применения ЛС», «остеопороз» (в русском и английском варианте, соответственно), а также соответствующих MeSH терминов.

Результаты. Рассмотрен опыт применения системы DRP в сфере здравоохранения разных стран, изучены факторы риска возникновения проблем, связанных с применением ЛП, соответствующие вмешательства при выявлении высоких значений DRP. Исследования проблем, связанных с применением ЛП для лечения ОП при проведении комплексной фармакотерапии, позволили определить целесообразность использования данного метода в целях повышения безопасности и эффективности проводимого лечения у пациентов.

Заключение. Анализ возникающих DRP позволяет повысить приверженность пациентов к лечению и купировать возникающие НР, что улучшает качество жизни пациентов и повышает результативность проводимой фармакотерапии. Внедрение такого метода исследования безопасности ЛП в систему фармаконадзора Российской Федерации является важным шагом в развитии персонализированной медицины. Дальнейшее изучение проблем, связанных с применением ЛП, у пациентов с ОП также позволит снизить риски, возникающие при проведении комбинированной фармакотерапии.

Ключевые слова: проблемы, связанные с применением лекарственных препаратов; остеопороз; нежелательные реакции; фармаконадзор

Список сокращений: НР – нежелательная реакция; ЛП – лекарственный препарат; ЛС – лекарственное средство; ОП – остеопороз; DRP – проблемы, связанные с применением лекарственных препаратов; PCNE – Европейская сеть фармацевтической помощи.

INTRODUCTION

According to the International Classification of Diseases, the 10th Revision[1], musculoskeletal diseases are a group of syndromes and nosological forms caused by lesions of the musculoskeletal system structure of an inflammatory and metabolic nature [1]. These diseases have a significant negative impact on the economy, labour and psychological potential of the modern society [2]. This group of diseases occupies one of the leading positions in the morbidity structure of the

[1] The International Classification of Diseases 10th Revision (ICD-10). Available from: https://icd.who.int/browse10/2019/en

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adult population of the Russian Federation. It is second only to the diseases of the circulatory and respiratory systems[2] [3]. The increase in primary and general morbidity of the population caused by the diseases of the musculoskeletal system, as well as high rates of invalidity and temporary disability due to the pathology of this organ system, make the problem of treatment and prevention of this group of diseases a priority of public health in the Russian Federation [4], especially in connection with a wide involvement of different age groups and a long-term rehabilitation [5].

Osteopathies and chondropathies account for only about 2% of the total number of diseases of the musculoskeletal system [3]. These low rates can be explained, on the one hand, by limited possibilities to diagnose the disease in many subjects of the Russian Federation, and on the other hand, by a long, invisible development of the disease, which leads to the late patient encounter for medical care [1].

Osteoporosis (OP) is a metabolic disease of the skeleton characterized by a decrease in the bone mass, impaired bone microarchitectonics and, as a consequence, a possibility of the fracture development even in case of minimal injury[3] [6]. Leading to millions of fractures worldwide annually, as well as to the deterioration of physical and psychological health, a quality of life, and a shortened life expectancy, this disease represents a serious global health problem [7–9]. OP is a common disease in the Russian Federation [10–12]; according to some estimates, it affects about 14 million people, accounting for approximately 10% of the country's population [13]. A risk group for the occurrence of OP is mainly elderly patients. The prevalence of OP in this cohort of patients is caused not only by lifestyle and diet changes, but also by physiologic changes in the patient's body; all these are related to the activation of the immune system and the development of inflammation, which directly affects the density and quality of the bone tissue. Various pathogenic factors are involved in the pathogenesis of OP, such as the intestinal microbiome, autophagy, abnormal iron metabolism, aging, and stress [6]. In addition, a combination of biological, environmental, and behavioral factors plays a significant role in the development of OP. Biological factors include age, gender, genetics, and a postmenopausal syndrome. Behavioral and environmental factors include a diet poor in calcium, smoking, excessive alcohol consumption, hypodynamia, and a limited outdoor activity. The factors that affect the skeletal system through pathophysiologic or anatomic effects on bone structures and strength deserve a particular attention. Such factors are a bone mineral density, bone microarchitecture, skeletal geometry and a muscle mass [7].

The chronic nature of this disease determines the long-term pharmacotherapy of patients, which consequently increases the risk of adverse drug reactions (ADRs) during the use of medicinal products (MPs).

The identification of ADRs, as well as methods of their assessment, a prevention and reduction of risks of their development is the basis of the pharmacovigilance system[4], the conduct of which is mandatory for all subjects of the drug circulation[5].

Despite an annually increasing number of spontaneous ADR reports received by the Federal Service for Supervision in the Sphere of Healthcare (Roszdravnadzor) [14], the system of monitoring the efficacy and safety of drugs in Russia still faces some difficulties, such as a reduction in the number of regional centers for drug safety monitoring, which traditionally contain more detailed information [15]. There is also an insufficient number of periodic quality and safety reports received from pharmaceutical companies – marketing authorization holders [14]. Increased requirements to the quality of efficacy and safety monitoring, including those caused by the recent update of the EAEU Good Pharmacovigilance Practice[6], and the identified problems require the system improvement of the drug safety ensuring and control.

Drug-related problems (DRPs) are defined as events or circumstances related to a patient's use of a drug that actually or potentially interferes with the patient's ability to obtain the desired results from the use of the drug [16]. DRPs are associated with increased healthcare expenditure and patients' hospitalization ~~of~~, prolonged hospital stays, a decreased quality of life, and increased mortality. The occurrence of health problems in the presence of DRPs is a serious problem for both patients and the health care system. The economic costs to the government and patients caused by these problems are significant [17, 18]. The identification and study of DRPs, drug groups and individual drugs that have a high risk of drug-related problems play an important role in the therapy of patients, as they help to reduce the number of emerging ADRs and, therefore, the mortality of patients, as well as to increase the level of patient's adherence to the treatment [19]. The study

[2] Healthcare in Russia. 2023: Federal Service of State Statistics. Available from: https://rosstat.gov.ru/folder/210/document/13218

[3] World Health Organization (2007) Assessment of osteoporosis at the primary health care level. Summary Report of a WHO Scientific Group. WHO, Geneva. Available from: https://frax.shef.ac.uk/FRAX/pdfs/WHO_Technical_Report.pdf

[4] Decision of the Council of the Eurasian Economic Commission dated Nov 3, 2016 No. 87 (edited May 19, 2022) "On Approval of the Rules of Good Pharmacovigilance Practice of the Eurasian Economic Union". Russian

[5] Federal Law dated Apr 12, 2010 No. 61-FZ "On Circulation of Medicines". Russian

[6] Decision of the Council of the Eurasian Economic Commission dated Nov 3, 2016 No. 87 (edited May 19, 2022).

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of drug-related problems in the Russian Federation is practically not available. There are only a few scientific works dedicated to this problem [16, 20–22]. The study of the international experience in the use of DRP system to monitor the safety of drugs used for the treatment of chronic diseases, including OP, makes it possible to improve the existing approaches to the safe use of drugs, to conduct a more accurate and in-depth analyses of emerging ADRs and, as a result, can lead to the evolution of new and improved methods to prevent the development of adverse events.

According to Decree of the President of the Russian Federation No. 642[7] dated Dec 1, 2016, one of the priorities of the scientific and technological development of the Russian Federation is the transition to personalized medicine, high-tech healthcare and health-saving technologies, including the ones due to the rational use of drugs. The development and improvement of the pharmacovigilance system inevitably leads to an increase in the level of the rational use of drugs and the development of the healthcare, which highlights the relevance of this study.

THE AIM of the study was to review the available evidence on the application of a promising method of drug safety monitoring – the analysis of drug related problems (DRPs) system in the pharmacotherapy of OP.

MATERIALS AND METHODS

The authors independently selected the literature sources, and then made a collegial decision to include the article in the analysis. The following databases and search systems were used for studies by both Russian and foreign authors: PubMed, elibrary.ru, Google Scholar, CyberLeninka, and the Russian National Library. The information sources were searched using the following keywords and word combinations: “drug-related problems”, “drug safety”, “osteoporosis” (in Russian and English, respectively), as well as the corresponding MeSH terms[8]. The search period was from Jan 1, 1886, to Oct 31, 2023. The process of selecting studies dedicated to the DRP system in OP pharmacotherapy, following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 recommendations, is illustrated in Figure 1 [23].

RESULTS AND DISCUSSION

System for analyzing problems associated with MPs use

The term DRP was first introduced in a 1973 study, which defined the problems associated with the use of MPs as “any primary or secondary condition resulting from a non-medical use of an MP that causes an individual or their partners to seek medical advice” [24]. The concept of DRPs has evolved with the development of clinical pharmacy in the world public health service during the late 1980s and early 1990s [26]. Clinical pharmacy is a branch of pharmacy that involves clinical pharmacists providing a direct patient care to optimize the use of medication, promote patient well-being, and prevent diseases [25]. The problems related to the use of medication, have been categorized according to 8 parameters, such as an inappropriate drug prescribing for defined pathologies and illnesses resulting from the development of ADRs. Pharmacists are primarily responsible for detecting, managing the consequences of, and preventing DRPs. They should collaborate with healthcare providers to be involved in the patient care system [26].

Since the conception of the DRP system, the issue of unifying the classification of the ease of administration in practical healthcare has been considered a problem. In 1994, the Pharmaceutical Care Network Europe (PCNE) was established, which became the official association of pharmacists in Europe for joint research in pharmaceutical care of patients, including but not limited to the identification of problems related to the use of drugs in 2004[9]. PCNE develops, approves, and revises the DRP classification based on the continuous data from various medical institutions and pharmacists worldwide, not just in Europe.

The most widely used system for studying the incidence and severity of DRPs and analyzing the problems associated with MPs, is currently the DRPs system PCNE V.9.1[10] of 2020. This system is based on classifying DRPs into 5 major categories: P (Problems) – problems, C (Causes) – causes, I (Planned Interventions) – interventions, A (Intervention Acceptance) – acceptance of the intervention, and O (Status of the DRP, Outcomes) – consequences. The researcher can identify DRPs either by analyzing questionnaires from patients and physicians, or based on spontaneous ADR reports received from medical, pharmaceutical organizations, and marketing authorization holders. This system is convenient for use in clinical practice and is periodically updated based on the results of publications related to the use of MPs. The current version of the classification is free of charge and available for downloading on the official website of PCNE[11]. In 2021, DRP PCNE V.9.1[12] passed the second round of validation with the participation of 158 pharmacists from 12 countries.

[7] Decree of the President of the Russian Federation dated Dec 1, 2016. No. 642 “On the Strategy of Scientific and Technological Development of the Russian Federation”. Russian

[8] Medical Subject Headings, 2023. Available from: https://meshb.nlm.nih.gov

[9] Pharmaceutical Care Network Europe Foundation. Available from: https://www.pcne.org

[10] PCNE Classification for Drug-Related Problems V9.1. Available from: https://www.pcne.org/upload/files/417_PCNE_classification_V9-1_final.pdf

[11] Pharmaceutical Care Network Europe Foundation.

[12] PCNE Classification for Drug-Related Problems V9.1.

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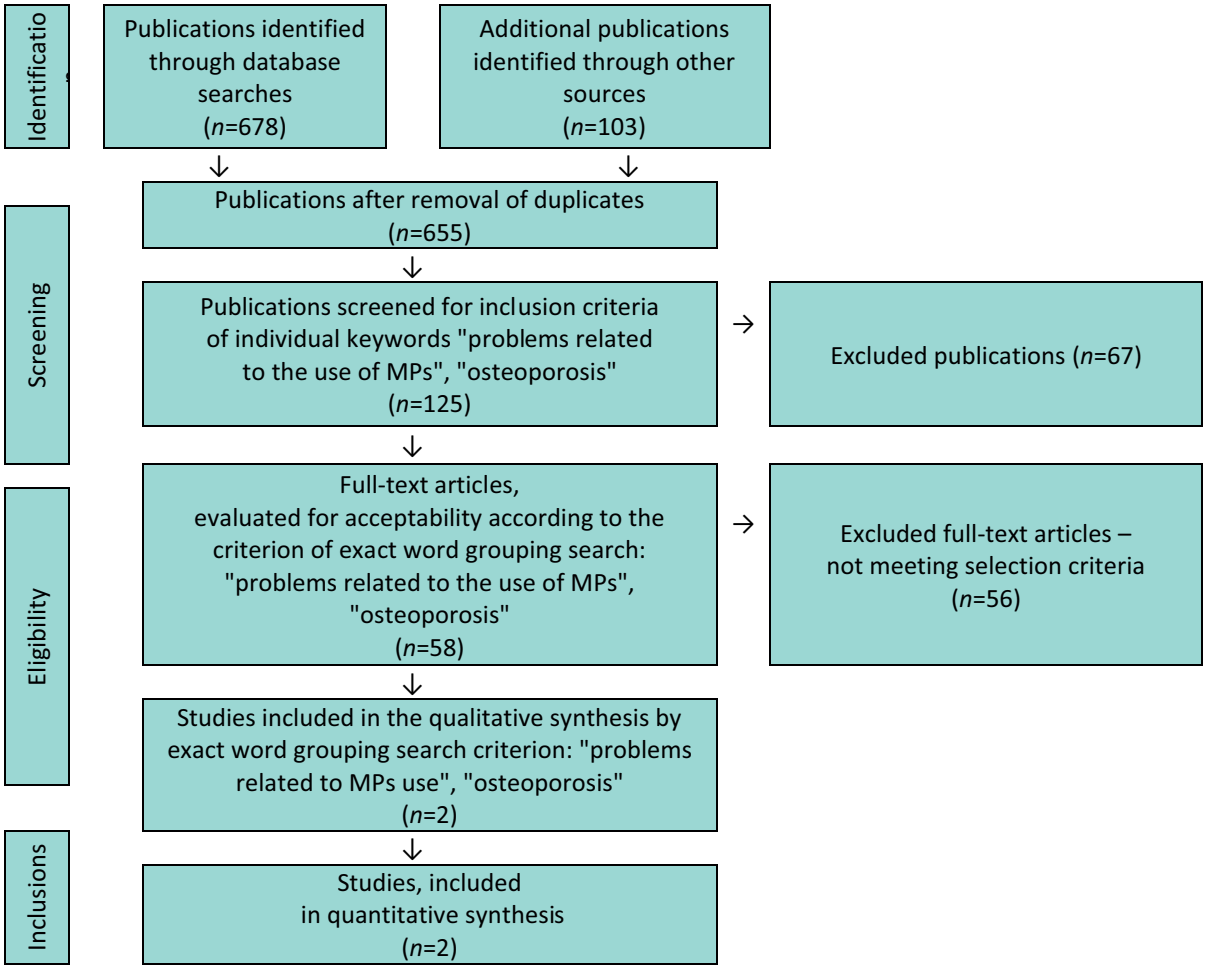

Figure 1 – PRISMA flowchart showing the number of publications selected in the study

Despite the above-mentioned impact that DRPs have on the health care system, most of these problems are predictable or potentially preventable [27, 28]. One of the methods to increase the detection of DRPs and, therefore, their prevention, is to include pharmacists in the patient care system [29–31]. The interventions described in the found out DRP studies, are quite diverse and cover a large number of aspects of therapy, such as problems of patient adherence to treatment, drug compatibility (interactions), and correction of prescribed doses of drugs [32–34].

Various factors may influence the manifestation of DRPs, for example, body characteristics such as a female gender, the age over 65 years, and differences in the knowledge of pharmacology among healthcare professionals, resulting in an increased risk of polypragmasy [35–37]. A variety of researchers have indicated a high risk of DRPs of MPs that have a predominantly renal route of excretion (anticoagulants or diuretics) [38, 39]. These clinical and pharmacological risk factors as well as the number of drugs used significantly, influences the number of detected DRPs [40].

The identification and characterization of drug-related problems, their causes, and the evaluation of concomitant interventions are of particular interest in daily clinical practice. This is especially true in hospital inpatient units of medical centers due to the high risk of iatrogenesis. To ensure a thorough evaluation of the issues related to the use of MPs, it is important to consider validated DRPs classification systems, representative samples, and sufficiently long study periods to draw valid conclusions [41].

Osteoporosis problem

OP is the most common metabolic bone disease [42, 43]. This disease is characterized by a low bone mineral density, which makes the affected bones vulnerable to fractures. As of 2019, about 42 million patients diagnosed with OP have been reported worldwide; some estimates suggest that this number may exceed 200 million by 2034 [44]. A large number of patients and a significant deterioration in the quality of patients' life require increased attention of the health care community to this pathology.

According to the International Classification of Diseases of the 10th revision, there are more than

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20 forms of OP[13]. The most common form of primary OP among them is postmenopausal OP, which is caused by a decrease in the estrogen secretion in the postmenopausal period [45]. Postmenopausal OP is diagnosed on the basis of the presence of a fragility fracture or a bone mineral density score of the spine, femur or its neck that is at least 2.5 standard deviations below the mean value in a control population of adults measured by densitometry [46]. After a femoral neck fracture, many women never recover the ability to move independently, 20% of patients undergo hospitalization, and the risk of patient's death within one year doubles compared to the pre-fracture period [47]. Women are highly predisposed to the development of OP and, therefore, to complications of it. This is due to a decreased secretion of progesterone, the amount of which decreases after reaching 40–45 years of age, and estrogen (the amount of which decreases at 45–52 years of age). Reaching the age of 27 years is considered a critical point of modern aging [48].

Based on various mechanisms of the bone homeostasis regulation, a number of pharmacological groups of drugs aimed at the treatment of osteoporosis in clinical practice, are as follows: bisphosphonates, selective estrogen receptor modulators, calcitonin, drugs of a molecular action, etc. The main drugs are MPs of a bisphosphonates group [49, 50]. Bisphosphonates are synthetic analogues of the endogenous regulator of bone mineralization – pyrophosphate. This group of drugs acts at the level of osteoclasts, disrupting their metabolism, adhesion of tumor cells to the bone matrix, thereby inhibiting their migration, invasion and angiogenesis. Bisphosphonates are often used in the treatment of metabolic bone diseases such as a bone mass loss caused by the use of glucocorticoids and other hormonal agents [51]. The main goal of treatment is to prevent fractures in high-risk patients before their first fracture (a primary prevention) or before a follow-up fracture (a secondary prevention) [47].

A maximal suppression of the bone resorption occurs approximately within 3 months after the start of the oral therapy with bisphosphonates taken on a daily, weekly, or monthly basis, and remains approximately constant throughout the treatment [51]. Despite the efficacy of this class of drugs in OP, manifested as a significant reduction in the risk of various fractures [52], they are characterized by the development of frequent, serious and severe ADRs – osteonecrosis of the jaw, the atrial fibrillation, atypical fractures of the femur [53–55], which, in turn, is the basis for additional monitoring of the safety of pharmacotherapy. The parenteral administration of bisphosphonates may be associated with the development of fever, headaches, an increased fatigue, muscle and bone pains [54].

[13] The International Classification of Diseases 10th Revision (ICD-10).

DRPs in osteoporosis pharmacotherapy

Based on the aforementioned classification of DRPs by PCNE V.9.1, a prospective study was conducted in a academic hospital in China to identify and analyze DRPs by a multidisciplinary team of professionals consisting of one physician and six pharmacists who were involved in a comprehensive pharmaceutical care program [56]. The data from 219 OP patients were included in the analysis. The information needed for the DRPs assessment, was obtained from electronic medical records, direct observations of patients during their physicians' visits. A total of 343 DRPs were identified, with a mean of 1.57 DRPs per patient. In the study sample, the most common DRPs were as follows: "treatment safety, P2" (66.8%; 229 cases), "other DRPs, P3" (21.0%; 72 cases), and "treatment efficacy, P1" (12.2%; 42 cases). The main causes of DRPs were "a dose choice, C3" (35.9%; 211 cases), "a process of drug use, C6" (28.9%; 170 cases), and "a drug choice, C1" (12.6%; 74 cases). A total of 711 interventions were proposed to resolve the DRPs encountered, with an average of 2.1 interventions for each reported DRP. Of the interventions undertaken by health care providers, 91.0% were fully implemented, leaving only 30 DRPs unresolved before a patient discharge.

In addition, it was found out that the number of concurrently taken drugs was statistically significantly associated with the number of DRPs (p=0.023). This can be explained by the fact that as the number of drugs increases, the probability of drug-drug interactions grows and the risk of medication errors rises. This is directly related to the occurrence of a large number of DRPs, so, polypragmasia patients should be given a timely assistance by health care providers to identify and resolve DRPs.

In the study presented above, the organizers also offered a comprehensive pharmacotherapy care program that included a pre-prescribing screening using specially designed software and pharmacists review of prescriptions, verification of a drug compatibility by clinical pharmacists, and a discussion of pharmacotherapy results by a multidisciplinary team (physicians and clinical pharmacists) before the patients had been discharged. The team also collected the data on DRPs and offered assistance to patients to resolve their problems: to reduce the dose or substitute the drugs. The pharmacists' recommendations related to the use of MPs, were effective, thereby improving the patient adherence to the treatment [56].

In Serbia, in Jan 2014, a prospective study was conducted among OP outpatients in three different medical centers [49]. The patients over 50 years of age were asked to answer open questions in an anonymous questionnaire. The study included 355 participants: 329 (92.7%) women and 26 (7.3%) men. The patients who had suffered at least one osteoporotic fracture (208 patients) were significantly less adherent

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to therapy, were less likely to engage in sports and regular physical activity, and were more likely to have a nutrition deficient in calcium and vitamin D than the patients without fractures (147 patients). The researchers have also found out that the effectiveness of the OP treatment is reduced as a result of a number of problems associated with the use of drugs that both physicians and patients face. These include the development of ADRs during the use of drugs, patients' preconceptions about the efficacy and safety of drugs, and non-compliance with physicians' recommendations regarding non-drug therapy (diet, regular exercises). It should be noted that a significant number of patients did not adhere to the direct recommendations of the doctors concerning the intake of drugs, which indicates a low adherence of patients to the treatment. The main reasons for refusal of pharmacotherapy mentioned by patients, were the occurrence of adverse effects (48.5% of the total number of patients who did not adhere to the prescribed therapy), the belief that the drugs for the OP treatment cause more harm than benefit (68.9%), neglecting the impact of OP and its complications on the general state of health (57.3%) [57].

Despite the advantages and benefits of using the PCNE classification system, there is currently no equally convenient method for all researchers to analyze DRPs. In a study conducted in Finland, the authors pointed out the inconsistency of existing disease and intervention classification systems with emerging DRPs. Therefore, the researchers adapted the DRP classification by adding the causes of DRPs and the interventions to manage these problems [58]. It is worth noting that, due to such studies; the above-mentioned PCNE classification is periodically updated, supplementing the existing classification with necessary items.

CONCLUSION

The reviewed studies have identified the feasibility of using MPs to improve the safety and effectiveness of treatment during the complex OP pharmacotherapy. It is important to note that the use of MPs should be carefully evaluated and monitored.

The introduction of the modern method of drug safety research into the pharmacovigilance system of the Russian Federation is considered an important step in the development of personalized medicine. Further research into the problems associated with the drug use in OP patients will help reduce the risks associated with mono- and combination pharmacotherapy. It is important to remember that these risks may also be caused by age-related features of OP patients. These features include multimorbid polypragmasy, age-related physiological changes, and peculiarities of pharmacokinetics and pharmacodynamics of drugs. Therefore, detecting, analyzing, and preventing DRPs occurrence in OP patients is crucial in improving patients' adherence to the treatment, the effectiveness of pharmacotherapy, and ultimately, their quality of life.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTION

All authors have made equivalent and equal contributions to the publication. All authors confirm that their authorship meets the ICMJE international criteria (all authors made substantial contributions to the conceptualisation, literature search and preparation of the article, read and approved the final version before the publication). Elena A. Egorova – idea and planning of the paper structure, design of graphic material, writing the article; Asan M. Beitullaev – collection of material and writing of the draft manuscript; Alexander V. Matveev – literature analysis, writing the article; Ksenia N. Koryanova – analysis, editing and approval of the final version of the manuscript.

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