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Particularities of ensuring with medicines the patients with rare diseases in the Republic of Moldova

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Abstract

Background: To ensure rare disease patients with medicines is a challenge for the health system. Treatments for rare diseases are very expensive, so the main financial burden for providing patients with medicines lies with the state. The objective of the study was to identify the aspects related to the optimization of process of assurance with medicines the patients with rare diseases.
Material and methods: Retrospective study was performed using systemic analysis methods. Data were collected and processed with reference to health programs in the field of rare diseases and centralized public procurement.
Results: The mechanism by which "rare" patients are provided with medicines and major problems related to was analyzed. The National Program "Combating rare diseases" represents the first stage by identifying the rare diseases that most frequently affect patients in the Republic of Moldova. Treatment options and annual medicines requirements are set in accordance with national clinical protocols and international guidelines recommendations, the number of patients on the doctor's records, as well as statistical data.
Conclusions: Major problems in ensuring medicines to patients with rare diseases have been identified. The need of medicines is ensured by centralized public procurement, from the financial resources of the state budget, which were analyzed for the period of years 2018-2020.
Key words: rare diseases, health programs, public procurement.

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Introduction

Rare diseases, by definition, affect few people, but have a major impact on public health, being highlighted by the lack of relevant treatments or their cost-inefficiency, becoming financially unviable for health domain [1, 2]. However, the health care of all patients is a value element of the right to health protection, being so a fundamental principle in a modern state. [3]. Thus, the problem of medical and pharmaceutical assistance for people suffering from rare diseases has become one of the most difficult in the modern medicine. In these circumstances, rare diseases are recognized as an important issue in the field of public health and in the budget allocation in healthcare. So, over time, the need to ensure an equitable access to patients' treatment, regardless of the prevalence of the disease, has become a fundamental premise in creating policies and strategies supporting the multilateral development of the field [4-7].

Material and methods

The objective of the study was to identify the aspects related to the optimization of process of assurance with medicines the patients with rare diseases in the Republic of Moldova. For data collection, a retrospective study using systemic analysis methods was performed. Data were collected and processed with reference to health programs in the field of rare diseases and centralized public procurement. The National Program "Combating Rare Diseases" was identified and analyzed according to the following criteria: rare diseases included, medicines selected for the treatment of patients, the need of medicines for the years 2018-2020 and procurement through tenders.

Results and discussion

Organizing medical and pharmaceutical assistance for patients with rare diseases in the Republic of Moldova remains difficult because of the lack of a patient's registry, standards for the diagnosis and treatment of patients and inaccessibility of medicines. Therefore, many patients suffering from rare diseases cannot receive the necessary care. Also, it should be pointed out that medicines for the treatment of rare diseases are very expensive and the main financial burden for providing patients with the necessary medicines lies with the state.

The State guarantees the health protection of citizens, regardless of gender, age, presence of diseases, conditions, property and official status, the residence and other circumstances. Under the program of "State guarantees", citizens

are provided with free healthcare, according to the list of diseases, whose treatment is reimbursed by the state.

The obligation to provide the rare disease patients with costless medicines is assigned to the component entities of the State, which are authorized to organize the medical care provided by the legislation of the Republic of Moldova for certain categories of citizens. They facilitate the accessibility of medicines to citizens and organize the supply of medicines included in the lists and registers of people entitled to receive state assistance as provided by law.

National programs are an organized set of activities and services, established by law in order to prevent and treat diseases with serious consequences for the health of population and, in some cases, with increased epidemiological risk. Prophylactic activities and the specific treatment of these diseases are financed from the state budget.

The national programs are designed, implemented and coordinated by the Ministry of Health, Labor and Social Protection. Their objectives are established by the same institution together with the National Health Insurance Company, representatives of professional scientific medical associations, university clinics, research units and others.

The national program for rare diseases could solve many problems of the targeted patients. In this context, the Government of the Republic of Moldova adopted Decision no 636 of December 11, 2019, on the approval of the Government Action Plan for the years 2020-2023, in which to the part no VI "Social protection and health protection", was included the point 6.13 "Intensification of measures to prevent communicable and non-communicable diseases", listing the development and approval of a new National Program for Rare Diseases, to be completed by September 2021 [8].

Likewise, in 2019, the Ministry of Health, Labor and Social Protection ordered the list of rare diseases, current for the Republic of Moldova.

At present, there are 12 health programs at the national level, including the National Program "Combating Rare Diseases", which aim to significantly improve the quality of care for "rare" patients and to solve the rare disease problems in the Republic of Moldova. In order to carry out the health programs, the Ministry of Health, Labor and Social Protection together with the Center for Centralized Health Procurement organize tenders for the procurement of specific medicines and sanitary materials for consumption in hospitals and outpatient, in compliance with legal provisions on public procurement.

The National Program "Combating Rare Diseases" has been running for several years. The treatment of rare diseases began to be partially reimbursed from the budget of national programs in 2012. Then, 2 million 291 thousand lei were allocated for patients diagnosed with Wilson-Konovalov, cystic fibrosis, phenylketonuria and pituitary insufficiency diseases. In the subsequent years, the treatment for patients suffering from ß-thalassemia, early puberty, bullous epidermolysis and juvenile arthritis was also reimbursed. The volume of financial sources, allocated for the rehabilitation of the patients, also increased to over seven million lei in 2017 and 12 million lei in 2018. In 2020, for the diagnosis and treatment of rare diseases was planned over 39 million lei from the state budget, which is 15 million lei more compared to the amount provided for 2019 [9-10].

In 2020, the National Program "Combating Rare Diseases" includes 15 rare diseases, such as Wilson-Konovalov, phenylketonuria, juvenile arthritis, ß-thalassemia, hemophilia, pituitary insufficiency, early puberty, bullous epidermolysis, epilepsy, diabetes insipidus, Addison's disease, nonspecific ulcerative colitis / Crohn's disease, pulmonary hypertension, Duchenne muscular dystrophy and infectious diseases as cholera, malaria, toxoplasmosis.

Table 1

Medicines introduced in the National Program "Combating Rare Diseases" and selected according to the approved national clinical protocols

No	National clinical protocol	Recommended medicines to be used in the treatment of the rare disease	The presence of medicine in the list of essential medicines
1.	PCN-7 Idiopathic juvenile arthritis [11]	Tocilizumab, 80 mg/4 ml, vial	Section 2.4. Antirheumatics
2.	PCN-243 ß-thalassemia in children [12]	Deferoxamine, 500 mg, lyophilized powder	Section 4.2. Non-specific medicines used in intoxications
3.	PCN-108 Hemophilia in children [13]	Coagulation factor VIII, 500 IU, lyophilized powder	Section 11. Blood products and plasma substitutes
		Coagulation factor IX, 500 IU, lyophilized powder	
4.	PCN-191 Hemophilia in adults [14]	Coagulation factor VIII, 1000 IU, lyophilized powder	
		Coagulation factor IX, 1000 IU, lyophilized powder	
5.	PCN-290 Epilepsy in adults [15]	Levetiracetam, 500 mg, tablets	-
		Levetiracetam, 250 mg, tablets	-
6.	PCN-258 Wilson's disease in children [16]	D-Penicillamine, tablets	-
		Zinc Sulphate, tablets	-

Clear and detailed scales are needed to make clinical decisions about diagnosing and treating such diseases. These are implemented by elaboration of clinical protocols that have a double beneficial effect: on the one hand it gives patients a quality and optimal standard, and on the other hand, it gives the doctor protection in the decision-making process. The national clinical protocols are developed on the basis of international guidelines based on evidence of clinical and economic efficacy.

The list of rare diseases included in the National Program "Combating Rare Diseases" contains only six diseases for which national clinical protocols are developed, this representing the clinical basis in the process of establishing the diagnosis and choosing the treatment. Approved clinical protocols were consulted in the following rare diseases (tab. 1).

Also, in table 1 it is highlighted that the medicines selected for the listed diseases, except Levetiracetam, D-Penicillamine and Zinc Sulphate, are included in the list of essential medicines, approved by the Order of the Ministry of Health of the Republic of Moldova No 162 of April 23, 2007 and amended by the Order of the Ministry of Health of the Republic of Moldova No 144 of February 28, 2011, which ensures the access to healthcare [17, 18].

In other cases, international guidelines and protocols were consulted to determine the medication. So, the list of medicines for the treatment of patients with rare diseases is elaborated according to the national clinical protocols and international guidelines and protocols, and the need for medicines to be purchased is calculated based on statistical data on the number of "rare" patients registered. Thus, in accordance with the provisions of the Order of the Ministry of Health, Labor and Social Protection No 948 of August 10, 2018 on the organization of centralized procurement, the Ministry of Health, Labor and Social Protection submits to the Center for Centralized Health Procurement the need of medicines for the implementation of National Programs and treatment of rare diseases, according to the established diseases list.

According to the comparative analysis of the results of tenders organized for the procurement of medicines within the National Program "Combating rare diseases", for the years 2018 - 2020 (the first 5 months of the year), the following data were obtained:

1. For 50 patients with Wilson's disease, during the analyzed period, constant quantities of medicines according to the protocol were purchased;

2. 123 patients with phenylketonuria were provided with increasing amounts of nutrients free of phenylalanine and low in protein. Thus, in 2020, phenylalanine-free protein substitutes were purchased 3 times as much as in 2018, low protein pasta and flour 4 times and, respectively, 6 times as much as in 2018. In 2020, 4 new positions of nutrients were purchased (tab. 2).

3. Medicines for the treatment of juvenile arthritis, hemophilia in children, pituitary insufficiency, early puberty and diabetes insipidus were purchased annually in unchanged quantities or slightly fluctuating quantities as in the case of bullous epidermolysis;

Table 2

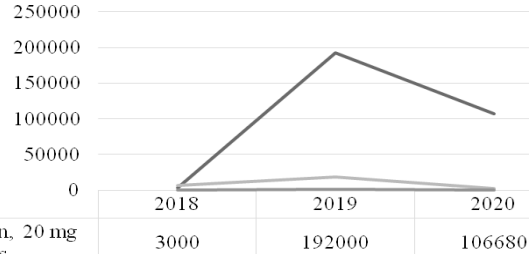
Nutrients purchased for patients with phenylketonuria

No	Nutrients	Contracted quantity (kg)		
		2018	2019	2020
1.	Phenylalanine-free substitutes with different protein content	436.5	986.0	1344.0
2.	Low protein flour	327.0	1890.0	2262.0
3.	Low protein pasta	500.0	2160.0	2145.0
4.	Low protein rice	-	-	900.0
5.	Milk substitute, low protein drink	-	-	260.0
6.	Low protein biscuits	-	-	1296.0
7.	Low protein egg substitute (powder)	-	-	162.0

4. In the case of thalassemia, there is a considerable decrease of about 800% in the amount of Deferoxamine purchased and a decrease of about 600% in the amount of Levetiracetam purchased in the years 2019-2020, for the treatment of patients with epilepsy;

5. In adult hemophilia, coagulation factor VIII was achieved in 2019 1.5 times as much as in 2020, and the quantity of coagulation factor IX – decreased by 2 times;

6. Medicines for the treatment of Addison's disease were purchased in quantities that differ from year to year, with a maximum in 2019 (fig. 1);



	2018	2019	2020
Hydrocortison, 20 mg tablets	3000	192000	106680
Fludrocortison, 100 mcg tablets	7000	18800	1800
Hydrocortison, injectable suspension 25 mg/5 ml, ampoules	0	1075	0

Fig. 1. Medicines purchased for the treatment of patients with Addison's disease, 2018-2020

7. Larger quantities of medicines were purchased for the treatment of pulmonary hypertension in 2020 compared to 2019, which is explained by the increase in the number of patients;

8. The biologic medicine Golimumab (300 pre-filled syringes for 30 patients with nonspecific ulcerative colitis) was purchased for the first time in 2020, as well as medicines for patients with Duchenne muscular dystrophy and for the treatment of infectious diseases such as cholera, malaria and toxoplasmosis.

The procurement of medicines within the program is done through tenders, announced by the order of the Ministry of Health, Labor and Social Protection. The Center for Centralized Health Procurement organizes public ten-

ders in order to conclude a state contract for the supply of medicines as a part of the implementation of the decision. The evaluation of the offers and the award of the contract is done by each position of medicine at the lowest price without VAT.

According to the results of the tenders published on the website of the Center for Centralized Health Procurement, for the concluded contracts, the following amounts were allocated: for 2018 year – 5 million 895 thousand lei, for 2019 – 5 million 194 thousand lei, and for 2020 – 28 million 678 thousand lei (calculated for the first 5 months of the year).

In the treatment of rare diseases are used both medicines that have the status of orphans and authorized medicines, without orphan designations, but which have included in the indications a rare disease.

Following this aspect, it was performed a comparative analysis of the list of medicines for the treatment of rare diseases, authorized in the European Union and the list of medicines proposed for the treatment of "rare" patients in the Republic of Moldova. Therefore, the medicines included in the National Program "Combating rare diseases", which are also found in the European list, such as tocilizumab, coagulation factor VIII and IX, somatropin, levetiracetam, golimumab, sildenafil, bosentan, iloprost and hydrocortisone were highlighted.

Conclusions

To facilitate the access to orphan medicinal products or medicines with rare disease indications and to build an infrastructure with all the necessary elements to support affected patients, it is necessary to develop, adopt and implement strategies and policies at national level, which, from the experience of other states, have positive results. In the Republic of Moldova, the State guarantees the protection of the health of patients with rare diseases through the National Program "Combating Rare Diseases". Patients suffering from the rare diseases included in the list of diseases of the Program and who are registered by a specialist, receive free medicines, reimbursed from the state budget, within the limit of purchased quantity.

However, during the study, major problems were stressed in the process of providing medicines to patients with rare diseases, such as:

– The lack of necessary medicines in the list of current rare diseases, as well as the absence of a common register of patients affected by rare diseases, making it impossible to analyze priorities in selecting diseases for inclusion in the National Program, which could so deprive other patients of free treatment;

– The absence of national clinical protocols for diseases included in the National Program, which aim to provide patients with qualitative and optimal treatment;

– The list of essential medicines that need regular updating and the assessment of the possibility of including several medicines for the treatment of rare diseases, thus ensuring safe access to care with effective and harmless medicines.

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Author's contribution
EZ conceptualized the idea, collected the data, wrote the manuscript, revised and approved the final text.

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Ethics approval and consent to participate
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Conflict of Interests
No competing interests were disclosed.