Original Study

HOSPITAL PHARMACOLOGY
International Multidisciplinary Journal

Hospital Pharmacology. 2023; 10(1):1250-1263

ISSN 2334-9492 (Online)
UDC: 615.218(497.11)"2009/2019";
615.218(48)"2009/2019"
doi:10.5937/hpimj2301250V

Comparative Analysis of The Consumption of Antihistamines for Systemic Use in The Republic of Serbia and Nordic Countries in The Period 2009-2019

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SUMMARY

Introduction: According to the ATC system of drug classification, group R06 includes H1 antihistamines for systemic use, which are divided into drug groups of the 1st and 2nd generation.

Aim: Since there are no national guidelines in Serbia, for treating most allergic diseases, our aim was to compare pharmaceutical products and treatment strategies of systemic antihistamines use in Serbia with that in the Nordic countries that have been recognized as countries with good pharmacoeconomic practice.

Material and methods: Data on drug consumption in the Republic of Serbia, the Kingdom of Norway, the Republic of Finland, and the Kingdom of Denmark were collected from the publications of national drug regulatory agencies for the period from 2009 to 2019.

Results: Loratadine was the most commonly consumed antihistamine in Serbia in 2009, making 72.32% of the total consumption of drugs in the R06 group. During observed period the consumption of cetirizine increased 21.8 times, levocetirizine increased 36.6 times, desloratadine increased 2.6 times. The most commonly used antihistamines in Serbia in 2016 were: loratadine with 34.86%, followed by desloratadine with 18.70%, and ketotifen with 14.52% of the total consumption of drugs in the R06 group. In 2019, the most commonly used antihistamines were levocetirizine, loratadine, desloratadine and cetirizine. In Norway as well as in Finland and Denmark, during all eleven years (2009-2019) cetiri-

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zine was the most consumed antihistamine with mild increase trend in consumption of 1.5-5.74-20.5%. The second most consumed antihistamine in Norway and in Finland was desloratadine and in Denmark, fexofenadine. A decrease in consumption was recorded in case of loratadine in all three Scandinavian countries. First generation antihistamines promethazine and dexchlorpheniramine showed a continuous but minimal downward trend.
Conclusion: Unlike Norway, Sweden and Denmark, in Serbia in the last 11 years, the consumption trends of antihistamines have not been consistent and seem to depend on various factors such as price.

Keywords: Antihistamines, Pharmacoeconomics, Consumption, ATC

INTRODUCTION

Drugs from the group of H1 antihistamines are competitive antagonists of histamine at postsynaptic H1 receptors. According to the anatomical-therapeutic-chemical (ATC) system of drug classification, group R06 includes antihistamines for systemic use, both oral and parenteral [1]. H1 antihistamines are divided into drug groups of the 1st and 2nd generation. The main difference between these two generations is that the first generation drugs cross the blood-brain barrier and lead to sedation, while the second generation drugs do not significantly cross the blood-brain barrier due to less lipophilicity. Also, antiemetic and anticholinergic effects are more pronounced in the first generation, and this generation of drugs is indicated for the prevention of nausea, vomiting and/or dizziness in kinetosis, symptomatic therapy of nausea and vomiting in Meniere's disease and other vestibular disorders, as well as short-term insomnia therapy. Representatives of both generations of antihistamines are indicated for the alleviation of nasal and ocular symptoms in seasonal and non-seasonal perennial allergic rhinitis, prevention of allergic reactions during hyposensitization therapy, symptomatic therapy of drug and food allergies, alleviation of chronic idiopathic urticaria, alone or in combination with other anti-inflammatory drugs in patients with atopic symptoms, therapy of pruritus of various origins: endogenous pruritus, eczema, dermatosis followed by itching, insect bites, viral exanthems, urticaria, etc [2,3].

Side effects related to the central nervous system and anticholinergic effects are more common with first generation drugs. Sedative effects are generally undesirable in the treatment of allergies, however, sometimes sedation can be beneficial (e.g. in young children before bedtime, in anxious patients) [4]. Even under these circumstances, other effects on the central nervous system, such as dizziness and fatigue, are undesirable. Among the side effects caused by anticholinergic drugs, dry mouth is the most common, but blurred vision, constipation and urinary retention also occur.

First-generation drugs are chlorpheniramine, clemastine, dimenhydrinate, diphenhydramine, hydroxyzine, meclizine, promethazine and others. Second-generation drugs are cetirizine, levocetirizine, fexofenadine, loratadine, desloratadine, rupatadine, ebastine, bilastine and others [5].

It is also important to mention the pharmacokinetic advantage of second-generation antihistamines, with the elimination half-life from 12 h to 24 h and thus more convenient dosing regimen, usually once a day, which resulted in better compliance compared to first-generation ones with more frequent dosing regimens [6].

AIM

The aim of this study was to compare pharmaceutical products and treatment strategies of systemic antihistamines use in Serbia with the countries that have been recognized as countries with good pharmacoeconomic practice. The consumption of drugs, from R06 group of ATC system of classification of drugs (antihistamines for systemic use) in the Republic of Serbia, for the period from 2009 to 2019, was analyzed and compared with the consumption of drugs from the same group, R06, in the Kingdom of Norway, the Republic of Finland and the Kingdom of Denmark, for the same period.

The second aim of this study was to investigate whether and how the price of the

antihistamines for systemic use affects their consumption in the Republic of Serbia.

MATERIAL AND METHODS

Data on drug consumption in the Republic of Serbia were collected from the publications of the Medicines and Medical Devices Agency of Serbia (ALIMS) on trade and consumption of drugs for human use, for each year during the observed period, from 2009 to 2019 [7-18].

Data on drug consumption in the Kingdom of Norway, the Republic of Finland and the Kingdom of Denmark were taken from the official websites of the Norwegian Institute of Public Health - *Folkehelseinstituttet* [18-20], the Finnish Drug Agency - *Fimea* [21] and the Danish Data Protection Agency - *Sundhedsdatastyrelsen* [22], respectively.

In accordance with the World Health Organization (WHO) guidelines of for drug consumption research [23], drug consumption is expressed by the methodology of defined daily doses (DDD), according to the ATC classification. DDD is the dose of active substance used in one day to treat the main indication in the adult population [24]. DDD is a statistical unit of drug consumption and does not depend on the price, dosage form, size or the package of the drug. The number of DDD per 1000 inhabitants/day provides insight into how many inhabitants (out of 1000) used the observed drug and were exposed to its influence during one day [8]. The results on the consumption of drugs from ATC group R06 are shown in the Tables, and expressed as DDD/1000 inhabitants/day and as a percentage of the total consumption of drugs in this group.

Impact of the price on drug consumption was investigated in Serbia. Statistical analysis was performed using SPSS Statistics, version 24 (IBM Corporation) and included linear regression analysis between consumption (expressed as DDD/1000 inhabitants/day) and price per DDD (expressed in RSD, official currency in Serbia) for each of 7 selected drugs during 2011-2019 consumed in Serbia. Only the 7 drugs that had data for all years were included in the linear regression analysis. Other drugs were not registered during the whole observed 9-year period. A p value of < 0.05 was considered statistically significant.

RESULTS

Consumption of antihistamines for systemic use (ATC group R06, subgroups and individual drugs) in the Republic of Serbia, Kingdom of Norway, Republic of Finland and the Kingdom of Denmark in the period from 2009 to 2019 are shown in Tables 1-4.

Loratadine was the most commonly consumed antihistamine in the R06 group In Serbia (Table 1), in 2009, when its consumption was 72.32% of the total consumption of drugs in the R06 group. In the following years, its consumption was variable with a declining trend. Compared to 2009, in 2019 its consumption decreased by 59.39%. The consumption of both cetirizine and levocetirizine was rising during the observed period. The consumption of cetirizine increased, from 0.11 to 2.40 DDD/1000 inhabitants/day, meaning that it increased 21.8 times. The consumption of levocetirizine remarkably increased, from 0.11 to 4.03 DDD/1000 inhabitants/day, i.e. it increased 36.6 times. Desloratadine showed a continuous increase in consumption in Serbia from 0.92 to 2.4 DDD/1000 inhabitants/day, or 2.6 times. In Serbia in 2016, the most commonly used antihistamines were loratadine with 34.86%, followed by desloratadine with 18.70% and ketotifen with 14.52% of the total consumption of drugs in the R06 group. In 2019, the most commonly used antihistamines were levocetirizine, loratadine, desloratadine and cetirizine.

In Norway (Table 2), during all eleven years (2009-2019) cetirizine was the most consumed antihistamine drug from the R06 group. Its consumption ranged from 33.14 to 36.49 DDD/1000 inhabitants/day, showing a mild increase trend of 5.74%. The second most consumed antihistamine in Norway was desloratadine, with consumption ranged from 3.98 to 26.95 DDD/1000 inhabitants/day and which showed the largest tendency of continuous increase of as much as 6.8 times from the first to the last year observed. Fexofenadine consumption increased 2.7 times, from 2.45 to 6.59 DDD/1000 inhabitants/day over the observed eleven-year period. A decrease in consumption was recorded in case of loratadine, from 9.24 to 5.88 DDD/1000 inhabitants/day, or by 36.36%. First generation antihistamines promethazine and dexchlorpheniramine showed a continuous but minimal downward tendency, while ebastine showed a small up-

Serbia												
Year	2009		2010		2011		2012		2013		2014	
ATC	DDD	%	DDD	%	DDD	%	DDD	%	DDD	%	DDD	%
R06	8.77	100.00	8.50	100.00	6.96	100.00	10.34	100.00	8.45	100.00	9.77	100.00
R06AA	0.29	3.29	0.11	1.27	0.07	1.04	-	-	0.15	1.73	0.16	1.59
R06AA02	0.29	3.29	0.11	1.27	0.07	1.04	0.08	0.82	0.15	1.73	0.16	1.59
R06AB	0.22	2.46	0.65	7.70	0.25	3.66	0.01	0.08	0.08	0.90	0.00	0.00
R06AB03	-	-	-	-	-	-	-	-	-	-	0.00	0.00
R06AB04	-	-	0.36	4.21	0.00	0.02	0.01	0.08	-	-	-	-
R06AB06	0.22	2.46	0.30	3.49	0.25	3.64	-	-	0.08	0.90	-	-
R06AC	0.21	2.37	0.10	1.17	0.06	0.82	0.14	1.32	0.13	1.53	0.12	1.28
R06AC03	0.21	2.37	0.10	1.17	0.06	0.82	0.14	1.32	0.13	1.53	0.12	1.28
R06AE	0.22	2.54	0.49	5.71	0.79	11.29	1.05	10.16	1.27	15.03	0.86	8.79
R06AE07	0.11	1.31	0.24	2.81	0.28	4.06	0.22	2.10	0.48	5.68	0.71	7.31
R06AE09	0.11	1.23	0.25	2.90	0.50	7.23	0.83	8.06	0.79	9.35	0.14	1.48
R06AX	7.83	89.34	7.15	84.15	5.79	83.19	9.06	87.62	6.83	80.82	8.63	88.34
R06AX12	0.15	1.76	-	-	-	-	-	-	-	-	-	-
R06AX13	6.34	72.32	5.83	68.53	4.23	60.76	6.20	59.98	3.80	45.03	4.86	49.78
R06AX17	0.42	4.79	0.30	3.55	0.19	2.76	1.28	12.41	1.17	13.79	1.40	14.32
R06AX26	-	-	-	-	-	-	0.00	0.00	0.08	0.98	0.12	1.20
R06AX27	0.92	10.47	1.03	12.07	1.37	19.67	1.57	15.22	1.78	21.01	2.14	21.87
R06AX28	-	-	-	-	-	-	-	-	-	-	-	-
R06AX29	-	-	-	-	-	-	-	-	-	-	0.11	1.16

Year	2015		2016		2017		2018		2019	
ATC	DDD	%	DDD	%	DDD	%	DDD	%	DDD	%
R06	9.71	100.00	12.48	100.00	9.79	100.00	13.97	100.00	13.14	100.00
R06AA	0.18	1.90	0.23	1.82	0.21	2.19	0.13	0.96	0.20	1.53
R06AA02	0.18	1.90	0.23	1.82	0.21	2.19	0.13	0.96	0.20	1.53
R06AB	-	-	-	-	-	-	-	-	-	-
R06AB03	-	-	-	-	-	-	-	-	-	-
R06AB04	-	-	-	-	-	-	-	-	-	-
R06AB06	-	-	-	-	-	-	-	-	-	-
R06AC	-	-	0.11	0.91	0.13	1.28	0.07	0.50	0.20	1.53
R06AC03	-	-	0.11	0.91	0.13	1.28	0.07	0.50	0.03	0.21
R06AE	2.15	22.11	3.13	25.05	4.96	50.69	6.46	46.22	6.43	48.96
R06AE07	0.93	9.62	1.38	11.08	2.21	22.57	2.46	17.61	2.40	18.26
R06AE09	1.21	12.49	1.74	13.97	2.75	28.12	4.00	28.62	4.03	30.70
R06AX	7.38	76.00	9.02	72.22	4.49	45.84	7.31	52.31	6.48	49.30
R06AX12	-	-	-	-	-	-	-	-	-	-
R06AX13	3.55	36.62	4.35	34.86	1.56	15.96	3.07	21.94	2.58	19.61
R06AX17	1.53	15.78	1.81	14.52	0.30	3.04	0.12	0.85	0.27	2.08
R06AX26	-	-	0.11	0.88	0.06	0.59	0.09	0.61	0.09	0.70
R06AX27	2.01	20.75	2.33	18.70	2.07	21.13	2.25	16.13	2.40	18.27
R06AX28	-	-	-	-	-	-	0.26	1.87	0.48	3.64
R06AX29	0.28	2.86	0.41	3.26	0.50	5.12	1.53	10.92	0.66	5.00

Table 1. Consumption of antihistamines for systemic use in Serbia, in the period from 2009 to 2019.

R06 - Antihistamines for systemic use
R06AA - Aminoalkyl ethers
R06AA02 - diphenhydramine
R06AB - Substituted alkylamines
R06AB03 - dimetindene
R06AB04 - chlorphenamine
R06AB06 - dexbrompheniramine
R06AC - Substituted ethylene diamines
R06AC03 - chloropyramine
R06AE - Piperazine derivatives
R06AE07 - cetirizine
R06AE09 - levocetirizine
R06AX - Other antihistamines for systemic use
R06AX12 - terfenadine
R06AX13 - loratadine
R06AX17 - ketotifen
R06AX26 - fexofenadine
R06AX27 - desloratadine
R06AX28 - rupatadine
R06AX29 - bilastine

Table 2. Consumption of antihistamines for systemic use in Norway, in the period from 2009 to 2019.

R06 - Antihistamines for systemic use
R06AA - Aminoalkyl ethers
R06AA09 - doxylamine
R06AB - Substituted alkylamines
R06AB02 - dexchlorpheniramine
R06AD - Phenothiazine derivatives
R06AD01 - alimemazine
R06AD02 - promethazine
R06AE - Piperazine derivatives
R06AE03 - cyclizine
R06AE05 - meclozine
R06AE07 - cetirizine
R06AE09 - levocetirizine
R06AX - Other antihistamines for systemic use
R06AX13 - loratadine
R06AX22 - ebastine
R06AX26 - fexofenadine
R06AX27 - desloratadine
R06AX28 - rupatadine
R06AX29 - bilastine

Norway												
Year	2009		2010		2011		2012		2013		2014	
ATC	DDD	%	DDD	%	DDD	%	DDD	%	DDD	%	DDD	%
R06	59.86	100.00	58.82	100.00	60.04	100.00	62.17	100.00	62.76	100.00	68.64	100.00
R06AA	-	-	-	-	-	-	-	-	-	-	-	-
R06AA09	-	-	-	-	-	-	-	-	-	-	-	-
R06AB	2.33	3.89	1.28	2.18	0.94	1.57	0.91	1.46	0.86	1.37	0.64	0.93
R06AB02	2.33	3.89	1.28	2.18	0.94	1.57	0.91	1.46	0.86	1.37	0.64	0.93
R06AD	4.64	7.75	4.66	7.92	4.64	7.73	4.47	7.19	4.36	6.95	4.42	6.44
R06AD01	3.02	5.05	3.09	5.25	3.13	5.21	3.07	4.94	3.03	4.83	3.08	4.49
R06AD02	1.61	2.69	1.57	2.67	1.51	2.51	1.40	2.25	1.34	2.14	1.34	1.95
R06AE	35.72	59.67	34.64	58.89	35.32	58.83	35.17	56.57	34.07	54.29	36.05	52.52
R06AE03	0.15	0.25	0.18	0.31	0.16	0.27	0.15	0.24	0.15	0.24	0.14	0.20
R06AE05	0.97	1.62	0.88	1.50	0.83	1.38	0.78	1.25	0.72	1.15	0.73	1.06
R06AE07	34.51	57.65	33.51	56.97	34.26	57.06	34.17	54.96	33.14	52.80	35.10	51.14
R06AE09	0.09	0.15	0.08	0.14	0.07	0.12	0.08	0.13	0.07	0.11	0.08	0.12
R06AX	17.18	28.70	18.24	31.01	19.16	31.91	21.61	34.76	23.46	37.38	27.53	40.11
R06AX13	9.24	15.44	8.74	14.86	8.79	14.64	7.94	12.77	7.08	11.28	7.29	10.62
R06AX22	1.52	2.54	1.57	2.67	1.66	2.76	1.56	2.51	1.56	2.49	1.56	2.27
R06AX26	2.45	4.09	3.24	5.51	3.58	5.96	3.59	5.77	3.91	6.23	4.41	6.42
R06AX27	3.98	6.65	4.69	7.97	5.12	8.53	8.53	13.72	10.91	17.38	14.27	20.79
R06AX28	-	-	-	-	-	-	-	-	-	-	-	-
R06AX29	-	-	-	-	-	-	-	-	-	-	-	-

Year	2015		2016		2017		2018		2019	
ATC	DDD	%	DDD	%	DDD	%	DDD	%	DDD	%
R06	68.54	100.00	70.17	100.00	73.60	100.00	75.94	100.00	79.02	100.00
R06AA	-	-	0.03	0.04	0.15	0.20	0.19	0.25	0.23	0.29
R06AA09	-	-	0.03	0.04	0.15	0.20	0.19	0.25	0.23	0.29
R06AB	0.36	0.53	0.19	0.27	0.16	0.22	0.16	0.21	0.14	0.18
R06AB02	0.36	0.53	0.19	0.27	0.16	0.22	0.16	0.21	0.14	0.18
R06AD	4.39	6.41	4.32	6.16	4.16	5.65	4.08	5.37	4.15	5.25
R06AD01	3.07	4.48	3.07	4.38	2.98	4.05	2.96	3.90	3.04	3.85
R06AD02	1.32	1.93	1.25	1.78	1.18	1.60	1.12	1.47	1.12	1.42
R06AE	34.51	50.35	34.89	49.72	35.30	47.96	35.64	46.93	37.43	47.37
R06AE03	0.16	0.23	0.16	0.23	0.17	0.23	0.03	0.04	0.01	0.01
R06AE05	0.77	1.12	0.65	0.93	0.76	1.03	0.86	1.13	0.86	1.09
R06AE07	33.50	48.88	34.00	48.45	34.29	46.59	34.68	45.67	36.49	46.18
R06AE09	0.08	0.12	0.07	0.10	0.08	0.11	0.07	0.09	0.07	0.09
R06AX	29.29	42.73	30.74	43.81	33.84	45.98	35.87	47.23	41.21	52.15
R06AX13	6.74	9.83	6.05	8.62	5.97	8.11	5.76	7.58	5.88	7.44
R06AX22	1.78	2.60	1.82	2.59	1.97	2.68	1.97	2.59	2.19	2.77
R06AX26	4.87	7.11	5.14	7.33	5.56	7.55	5.8	7.64	6.59	8.34
R06AX27	15.9	23.20	17.72	25.25	20.33	27.62	22.34	29.42	26.55	33.60
R06AX28	-	0.00	0.01	0.01	0.01	0.01	0.00	0.00	-	-
R06AX29	-	0.00	0.00	0.00	0.00	0.00	0.00	0.00	-	-

Finland												
Year	2009		2010		2011		2012		2013		2014	
ATC	DDD	%	DDD	%	DDD	%	DDD	%	DDD	%	DDD	%
R06	39.55	100.00	42.57	100.00	42.87	100.00	48.72	100.00	46.05	100.00	54.00	100.00
R06AE	25.07	63.39	26.96	63.33	26.95	62.86	30.37	62.34	27.99	60.78	31.18	57.74
R06AE03	0.05	0.13	0.09	0.21	0.09	0.21	0.10	0.21	0.10	0.22	0.10	0.19
R06AE05	0.21	0.53	0.17	0.40	0.17	0.40	0.16	0.33	0.15	0.33	0.14	0.26
R06AE07	19.50	49.30	21.29	50.01	21.60	50.38	24.41	50.10	22.64	49.16	25.38	47.00
R06AE09	5.22	13.20	5.32	12.50	5.02	11.71	5.68	11.66	5.10	11.07	5.56	10.30
R06AE53	0.10	0.25	0.08	0.19	0.07	0.16	-	-	-	-	-	-
R06AX	14.47	36.59	15.60	36.65	15.92	37.14	18.34	37.64	18.06	39.22	22.82	42.26
R06AX13	3.59	9.08	3.63	8.53	3.51	8.19	4.11	8.44	3.47	7.54	3.88	7.19
R06AX18	0.20	0.51	0.20	0.47	0.18	0.42	0.19	0.39	0.16	0.35	0.18	0.33
R06AX22	4.51	11.40	4.85	11.39	4.77	11.13	5.61	11.51	5.23	11.36	6.16	11.41
R06AX26	1.12	2.83	1.19	2.80	1.33	3.10	1.80	3.69	1.62	3.52	2.44	4.52
R06AX27	5.04	12.74	5.73	13.46	6.11	14.25	6.63	13.61	7.58	16.46	9.82	18.19
R06AX29	-	-	-	-	-	-	-	-	-	-	0.35	0.65

Year	2015		2016		2017		2018		2019	
ATC	DDD	%	DDD	%	DDD	%	DDD	%	DDD	%
R06	51.21	100.00	52.21	100.00	55.44	100.00	59.44	100.00	63.51	100.00
R06AE	29.53	57.66	28.81	55.18	31.36	56.57	32.45	54.59	34.31	54.02
R06AE03	0.10	0.20	0.07	0.13	0.07	0.13	0.05	0.08	-	-
R06AE05	0.15	0.29	0.14	0.27	0.14	0.25	0.15	0.25	0.19	0.30
R06AE07	24.37	47.59	23.74	45.47	26.62	48.02	27.51	46.28	29.40	46.29
R06AE09	4.91	9.59	4.86	9.31	4.53	8.17	4.74	7.97	4.73	7.45
R06AE53	-	-	-	-	-	-	-	-	-	-
R06AX	21.66	42.30	23.38	44.78	24.05	43.38	26.93	45.31	29.12	45.85
R06AX13	3.53	6.89	3.44	6.59	3.12	5.63	3.27	5.50	3.07	4.83
R06AX18	0.16	0.31	0.15	0.29	0.14	0.25	0.13	0.22	0.08	0.13
R06AX22	6.04	11.79	6.51	12.47	6.79	12.25	7.48	12.58	7.66	12.06
R06AX26	2.56	5.00	2.59	4.96	2.79	5.03	3.1	5.22	3.87	6.09
R06AX27	9.05	17.67	10.34	19.80	10.87	3.37	12.61	21.21	14.05	22.12
R06AX29	0.32	0.62	0.35	0.67	0.34	0.61	0.35	0.59	0.38	0.60

Table 3. Consumption of antihistamines for systemic use in Finland, in the period from 2009 to 2019.

R06 - Antihistamines for systemic use
R06AE - Piperazine derivatives
R06AE03 - cyclizine
R06AE05 - meclozine
R06AE07 - cetirizine
R06AE09 - levocetirizine
R06AE53 - cyclizine, combinations
R06AX - Other antihistamines for systemic use
R06AX13 - loratadine
R06AX18 - acrivastine
R06AX22 - ebastine
R06AX26 - fexofenadine
R06AX27 - desloratadine
R06AX29 - bilastine

Denmark												
Year	2009		2010		2011		2012		2013		2014	
ATC	DDD	%	DDD	%	DDD	%	DDD	%	DDD	%	DDD	%
R06	26.70	100.00	27.00	100.00	29.10	100.00	30.10	100.00	31.40	100.00	35.80	100.00
R06AA	0.30	1.12	0.30	1.11	0.30	1.03	0.20	0.66	0.20	0.64	0.30	0.84
R06AA02	0.20	0.75	0.20	0.74	0.20	0.69	0.20	0.66	0.20	0.64	0.20	0.56
R06AA04	0.10	0.37	0.10	0.37	0.10	0.34	0.10	0.33	0.10	0.32	0.10	0.28

Table 4. Consumption of antihistamines for systemic use in Denmark, in the period from 2009 to 2019.

R06 - Antihistamines for systemic use
R06AA - Aminoalkyl ethers
R06AA02 - diphenhydramine
R06AA04 - clemastine

R06AB - Substituted alkylamines
R06AB02 - dexchlorpheniramine
R06AC - Substituted ethylene diamines
R06AC01 - mepyramine
R06AD - Phenothiazine derivatives
R06AD02 - promethazine
R06AE - Piperazine derivatives
R06AE03 - cyclizine
R06AE05 - meclozine
R06AE07 - cetirizine
R06AE09 - levocetirizine
R06AX - Other antihistamines for systemic use
R06AX13 - loratadine
R06AX18 - acrivastine
R06AX22 - ebastine
R06AX26 - fexofenadine
R06AX27 - desloratadine
R06AX28 - rupatadine
R06AX29 - bilastine

R06AB	0.20	0.75	0.10	0.37	-	-	-	-	-	-	-	-
R06AB02	0.20	0.75	0.10	0.37	-	-	-	-	-	-	-	-
R06AC	0.00	0.00	0.00	0.00	-	-	-	-	-	-	-	-
R06AC01	0.00	0.00	0.00	0.00	-	-	-	-	-	-	-	-
R06AD	1.80	6.74	1.90	7.04	2.20	7.56	2.60	8.64	3.4	10.83	3.90	10.89
R06AD02	1.80	6.74	1.90	7.04	2.20	7.56	2.60	8.64	3.4	10.83	3.90	10.89
R06AE	13.50	50.56	13.80	51.11	15.00	51.55	15.30	50.83	15.50	49.36	17.30	48.32
R06AE03	0.50	1.87	0.50	1.85	0.60	2.06	0.60	1.99	0.50	1.59	0.50	1.40
R06AE05	0.20	0.75	0.20	0.74	0.10	0.34	0.10	0.33	0.10	0.32	0.10	0.28
R06AE07	11.80	44.19	12.30	45.56	13.50	46.39	13.80	45.85	14.10	44.90	15.90	44.41
R06AE09	0.90	3.37	0.90	3.33	0.80	2.75	0.80	2.66	0.70	2.23	0.80	2.23
R06AX	10.90	40.82	10.90	40.37	11.70	40.21	12.00	39.87	12.30	39.17	14.40	40.22
R06AX13	3.70	13.86	3.40	12.59	3.40	11.68	3.30	10.96	3.10	9.87	3.30	9.22
R06AX18	1.30	4.87	1.20	4.44	1.30	4.47	1.30	4.32	1.30	4.14	1.50	4.19
R06AX22	0.80	3.00	0.70	2.59	0.70	2.41	0.70	2.33	0.60	1.91	0.70	1.96
R06AX26	3.30	12.36	3.50	12.96	3.90	13.40	4.30	14.29	4.50	14.33	5.40	15.08
R06AX27	1.90	7.12	2.00	7.41	2.30	7.90	2.50	8.31	2.70	8.60	3.30	9.22
R06AX28	-	-	-	-	-	-	-	-	-	-	-	-
R06AX29	-	-	-	-	-	-	-	-	0.00	0.00	0.10	0.28

Year	2015		2016		2017		2018		2019	
ATC	DDD	%	DDD	%	DDD	%	DDD	%	DDD	%
R06	34.80	100.00	37.70	100.00	39.20	100.00	41.90	100.00	45.50	100.00
R06AA	0.30	0.86	0.30	0.80	0.30	0.77	0.40	0.95	0.40	0.88
R06AA02	0.20	0.57	0.20	0.53	0.20	0.51	0.30	0.72	0.30	0.66
R06AA04	0.10	0.29	0.10	0.27	0.10	0.26	0.10	0.24	0.10	0.22
R06AB	-	-	-	-	-	-	-	-	-	-
R06AB02	-	-	-	-	-	-	-	-	-	-
R06AC	-	-	-	-	-	-	-	-	-	-
R06AC01	-	-	-	-	-	-	-	-	-	-
R06AD	2.50	7.18	2.90	7.69	3.30	8.42	3.50	8.35	3.60	7.91
R06AD02	2.50	7.18	2.90	7.69	3.30	8.42	3.50	8.35	3.60	7.91
R06AE	17.50	50.29	18.70	49.60	19.10	48.72	20.20	48.21	21.60	47.47
R06AE03	0.60	1.72	0.60	1.59	0.70	1.79	0.60	1.43	0.10	0.22
R06AE05	0.20	0.57	0.10	0.27	0.10	0.26	0.10	0.24	0.50	1.10
R06AE07	16.00	45.98	17.30	45.89	17.70	45.15	18.80	44.87	20.50	45.05
R06AE09	0.70	2.01	0.70	1.86	0.70	1.79	0.70	1.67	0.60	1.32
R06AX	14.50	41.67	15.80	41.91	16.60	42.35	17.80	42.48	19.90	43.74
R06AX13	3.10	8.91	3.00	7.96	2.90	7.40	2.90	6.92	2.90	6.37
R06AX18	1.40	4.02	1.40	3.71	1.40	3.57	1.50	3.58	1.40	3.08
R06AX22	0.70	2.01	0.70	1.86	0.60	1.53	0.60	1.43	0.60	1.32
R06AX26	5.80	16.67	6.70	17.77	7.40	18.88	8.40	20.05	10.10	22.20
R06AX27	3.50	10.06	3.80	10.08	4.00	10.20	4.30	10.26	4.70	10.33
R06AX28	0.00	0.00	0.00	0.00	0.00	0.00	-	-	-	-
R06AX29	0.20	0.57	0.20	0.53	0.10	0.26	0.20	0.48	0.20	0.44

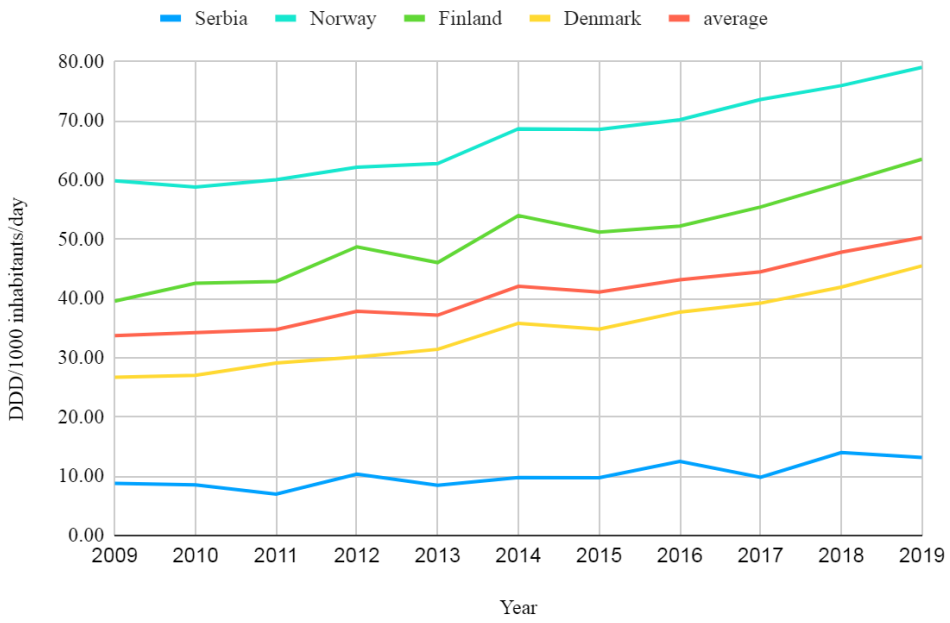

Figure 1. Total consumption of antihistamines for systemic use.

ward tendency in consumption.

In Finland (Table 3), during the eleven-year period (2009-2019), cetirizine was the most consumed antihistamine from the R06 group, with consumption increased from 19.5 in 2009 to 29.4 DDD/1000 inhabitants/day in 2019, or 1.5 times. An increase of consumption of desloratadine, the second most consumed antihistamine, was also recorded. Its consumption increased from 5.04 to 14.05 DDD/1000 inhabitants/day, or by 2.8 times. Fexofenadine and ebastine also showed an increase in consumption from 2009 to 2019, by 3.5 and 1.7 times, respectively. Levocetirizine and loratadine showed a mild downward tendency. The consumption of levocetirizine decreased from 5.22 in 2009 to 4.73 DDD/1000 inhabitants/day in 2019, while the consumption of loratadine decreased from 3.59 in 2009 to 3.07 in 2019 DDD/1000 inhabitants/day.

In Denmark (Table 4), the most consumed antihistamine was cetirizine, with consumption varying from 44.19% (2009) to 46.3% (2011) of total consumption of drugs in the R06 group. During the observed period its consumption was increasing, from 11.80 in 2009 to DDD/1000 inhabitants/day 20.50 in 2019. The second most consumed antihistamine, fexofenadine, also recorded an increase, from 3.30 in 2009 to 10.10 DDD/1000 inhabitants/day in 2019, or by 3.1 times. An increase in the consumption of desloratadine was recorded, from 1.90 to 4.70 DDD/1000 inhabitants/day, or by 2.5 times, as well as of promethazine, from 1.80 to 3.60 DDD/1000 inhabitants/day. A continuous mild decrease in consumption was recorded for loratadine, from 3.70 to 2.90 DDD/1000 inhabitants/day.

Figure 1 shows total consumption of antihistamines for systemic use (ATC group: R06) in the observed countries and the average consumption for them. In all four countries, the consumption of antihistamines for systemic use increased during the observed eleven-year period, between 2009 and 2019. In each year the highest consumption of antihistamines was recorded in Norway, varying from 59.86 (2010) to 79.02 (2019) DDD/1000 inhabitants/day. The other two Scandinavian countries had very similar upward and downward tendencies to Norway during the observed period, with lower DDD/1000 inhabitants/day values. Both in Finland and Denmark, the lowest consumption of antihistamines was recorded in 2009, and highest in 2019. In Finland 39.55 and 63.51 DDD/1000 inhabitants/day, and in Denmark 26.70 and 45.50 DDD/1000 inhabitants/day. The consumption of antihistamines in Serbia was 3 to 6 times lower compared to Scandinavian countries during the entire observed period. The consumption increased from 6.96 in 2011 to 13.97 DDD/1000 inhabitants/day in 2018. In Serbia, drops in the consumption of antihistamines were recorded in 2017 and 2019, while in Norway, Finland and Denmark the consumption increased in both years.

For drugs registered in Serbia a sim-

ple linear regression was calculated to predict consumption of different systemic antihistamines based on their price. A significant regression equation was found for loratidine ($F=9.563$, $p = 0.018$, $R^2 = 0.577$), ketotifen ($F=34.417$, $p = 0.001$, $R^2 = 0.831$) and desloratadin ($F=30.76$, $p = 0.001$, $R^2 = 0.815$). The results show that during 9 years' period, price of these three systemic antihistamines, significantly predicted their consumption (loratidine - $\beta=-0.760$, $p=0.018$; ketotifen - $\beta=-0.912$, $p=0.001$, desloratadine - $\beta=-0.903$, $p=0.001$). Considering the previous, we can say that increased consumption of loratadine, ketotifen and desloratadine is significantly associated with the decrease in their price. No statistically significant regression equation was found for other systemic antihistamines (levocetirizine - $F=3.438$, $p=0.106$, $R^2=0.329$; diphenhydramine - $F=2.757$, $p=0.141$, $R^2= 0.283$; cetirizine - $F=2.482$, $p=0.159$, $R^2= 0.262$; chloropyramine - $F=0.059$, $p=0.059$, $R^2=0.01$) (Figure 2).

DISCUSSION

The World Health Organization has recognized atopic disorders as a global health problem as numerous studies have demonstrated a sharp increase in the prevalence of asthma, allergic rhinitis (AR) and atopic dermatitis (AD) over the last four decades, particularly in children. The ISAAC study found that an increased incidence of allergic symptoms in children living in urban areas was associated with allergens in indoor environments and poor air

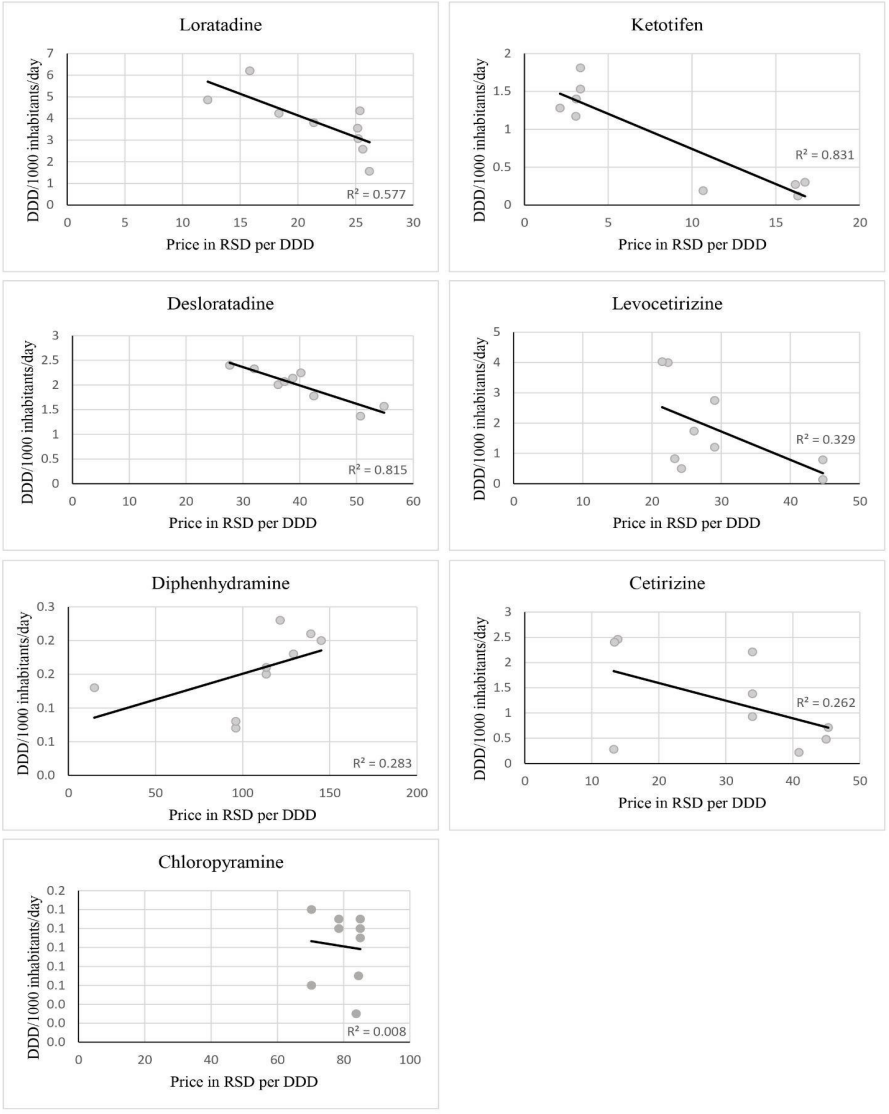

Figure 2. Linear regression analysis of price versus consumption of antihistamines for systemic use in the Republic of Serbia.

quality [25]. Since the 1950s, levels of certain indoor pollutants used as building materials and consumer products have changed drastically. These materials and products emit an array of chemicals, including solvents, unreacted monomers, and additives, that are nowadays ubiquitous [26]. Although the lack of objective exposure information limits the epidemiologic data, a meta-analysis reported that epidemiologic studies in children showed associations between indicators of phthalate exposure in the home and risk of asthma and allergies. The same study also concluded that heated PVC fumes could contribute to asthma development in adults [27].

It is not easy to compare data about the prevalence of allergically mediated diseases in different European countries. In most countries, if official data are available, a broad spectrum of allergic diseases is usually reduced to diseases and cases that had to be treated in a hospital. Most outpatient cases are self-medicated and are not recognized by the data. In addition, differences in prevalence may depend on the degree of awareness about allergic diseases, which may depend on the degree of „Westernization" of the country [28,29]. A cross-sectional study from 2018 based on a cohort of n=1530 school children in Sweden aged 13 to 14 reported that of all children, 32% (433/1333) reported at least one allergic disease [30].

Following an increase in the prevalence of allergies worldwide, the results of our study showed the expected increase in the consumption of antihistamines from year to year in all surveyed countries, Norway, Sweden, Denmark and Serbia. Consumption of antihistamines in Serbia was 3 to 6 times lower (from 6.96 to 13.97 DDD/1000 inhabitants/day) during the observed eleven-year period, which is explained by the lower prevalence of allergies compared to the Scandinavian countries. The European Federation of Allergy and Airway Diseases Patients Association (EFA), reported that in 2007. the prevalence of allergies in Norway, Denmark, and Finland was 30% [29]. In Serbia, on the other hand, in 2006, the incidence of allergies in the population aged 20 years and over was 5.3% [31]. The increase in the incidence of allergies in Serbia 8.1% in 2013 and 7.3% in 2019 [32,33] was consistent with the increase in antihistamines consumption. The results of this study showed that among all researched countries, second-generation antihistamines were more frequent, which is in line with the newest guidelines for treating allergic diseases in both the pediatric and adult population [34,35]. However, a different selection of the consumed second-generation antihistamines has been observed between the Scandinavian countries and Serbia. In the three Scandinavian countries, the most consumed antihistamine was cetirizine, while in Serbia, the most consumed were loratadine and levocetirizine. Among countries included in this study, only in Serbia, there were recorded relatively rapid than gradual changes in the consumption of antihistamines. In Serbia, there are no national guidelines for treating most allergic diseases, so general practitioners, as well as specialists that treat patients with allergic diseases, decide on which medicine to prescribe usually by their own experience or by the influence of local pharmaceutical management, which results in a huge variety, from year to year, among available antihistamines.

Also, most of the world's guidelines emphasize the use of the second generation of antihistamines but do not suggest which ATC antihistamine is precise [36-41]. Garg S. et al. conducted a survey which examined differences in antihistamines prescription among dermatology specialists and general practitioners/medical doctors of other specialties in treating atopic dermatitis. Even though the American Council for treating atopic dermatitis does not suggest the usage of antihistamines, Garg S. et al. research showed that dermatologists were the ones that prescribe the first generation of antihistamines more frequently than others and that they usually do that in a population younger than 21 y.o. [42]. Very little national statistical data of the countries enrolled in this study are available about the direct and indirect costs of respiratory allergies, particularly of allergic rhinitis. EFA survey, as well as available literature, showed that costs vary greatly from country to country, which refers to different reimbursement policies as well as the aforementioned awareness of having an allergic disease. Valovirta et al. found that indirect costs, which can be represented as time taking off due to allergic rhinitis, have affected one in every four working patients [43]. In the Scandinavian countries we selected, there was a similar pattern in the selection of specific antihistamines each year, which was in line with their existing guideline. On the other hand, in Serbia, there was no pattern in the selection of

a specific antihistamine during the observed period, so we expanded our research to analyze whether the price change is associated with the consumption of specific antihistamines.

Choosing a specific antihistamine is the first step in choosing the appropriate drug, but we should not forget the importance of the formulation itself. Most important are excipients with known effect (EKE) [44] and generally special attention is paid to excipients when the pediatric population is considered [45].

CONCLUSION

It is known that allergies have been increasing worldwide and that they affect many children and adults requiring more and more costs to both the health systems and individuals. Unlike Norway, Sweden and Denmark, in Serbia in the last 11 years, the consumption tendencies of antihistamines have not been consistent and seem to depend on various factors such as price, doctors' own experience or the influence of local pharmaceutical management. For three of the seven analyzed systemic antihistamines, the increase in the price of the drug was associated with a decrease in consumption (ketotifen, loratadine and desloratadine).

As choosing the right antihistamine is very important there is a need for making and following national guidelines for the treatment of allergically mediated diseases. It could be a step forward in improving therapy and reducing treatment costs, based on long-term benefits.

CONFLICTS OF INTEREST

All authors declare no conflict of interest.

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Komparativna analiza potrošnje antihistaminika za sistemsku upotrebu u Republici Srbiji i nordijskim zemljama u period 2009-2019.

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KRATAK SADRŽAJ

Uvod: Prema ATC sistemu klasifikacije lekova, grupa R06 obuhvata H1 antihistaminike za sistemsku primenu, koji su podeljeni u grupe lekova 1. i 2. generacije.
Cilj: Pošto u Srbiji ne postoje nacionalne smernice za lečenje većine alergijskih bolesti, želeli smo da uporedimo farmaceutske proizvode i strategije lečenja sistemske upotrebe antihistaminika u Srbiji sa nordijskim zemljama, koje su prepoznate kao zemlje sa dobro razvijenom farmakoekonomskom praksom.
Materijal i metode: Podaci o potrošnji lekova u Republici Srbiji, Kraljevini Norveškoj, Republici Finskoj i Kraljevini Danskoj prikupljeni su iz publikacija nacionalnih regulatornih agencija za lekove za period od 2009. do 2019. godine.
Rezultati: U Srbiji je loratadin bio najčešće konzumiran antihistaminik u 2009. godini, kada je njegova potrošnja iznosila 72,32% ukupne potrošnje lekova u grupi R06. Tokom posmatranog perioda potrošnja cetirizina je povećana 21,8 puta, levocetirizina 36,6 puta, desloratadina 2,6 puta. U Srbiji u 2016. godini najčešće korišćeni antihistaminici bili su loratadin sa 34,86%, zatim desloratadin sa 18,70% i ketotifen sa 14,52% ukupne potrošnje lekova u grupi R06. U 2019. godini najčešće korišćeni antihistaminici bili su levocetirizin, loratadin, desloratadin i cetirizin. U Norveškoj, kao i u Finskoj i Danskoj, tokom svih jedanaest godina (2009-2019) cetirizin je bio najkonzumiraniji antihistaminik sa blagom tendencijom povećanja potrošnje od 1,5-5,74-20,5%. Drugi antihistaminik po upotrebi u Norveškoj i Finskoj bio je desloratadin, a u Danskoj feksofenadin. Smanjenje potrošnje zabeleženo je u slučaju loratadina u sve tri skandinavske zemlje. Antihistaminici prve generacije prometazin i dekhlorfeniramin pokazali su kontinuiranu, ali minimalnu tendenciju pada.
Zaključak: Za razliku od Norveške, Švedske i Danske, u Srbiji u poslednjih 11 godina tendencija potrošnje antihistaminika je promenljiva i zavisi od različitih faktora poput cene.

Ključne reči: antihistaminici, farmakoekonomija, potrošnja, ATC

Received: February 23, 2023
Accepted: March 18, 2023