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RESEARCH ARTICLE

The Comparative Analysis of Asthma Treatment in Pediatric Patients of Russia and China

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Abstract

The correctly prescribed treatment regimen plays a key role in a successful control of asthma symptoms. Therefore, the monitoring studies aimed to facilitate rational medicine use for asthma treatment are relevant. The analysis of drug prescription patterns for asthma in pediatric outpatient care of Russia and China, as well as evaluation of the prescribed therapy conformity with the modern international standards on asthma treatment. This is a retrospective pharmacoepidemiological study on medical histories of asthma patients under the age of 18. The study involved 720 children's medical records (327 Russian and 393 Chinese) and prescribed medications for asthma within the period of 2018. The short-acting beta-2-agonists in Russia and China were typically prescribed as quick-relief drugs for treating asthma attacks in pediatric patients (in 78.6% and 83.7% of cases, respectively ($p > 0.05$)). Inhaled corticosteroids (in 65.1% of cases) and leukotriene receptor antagonists (in 18.6% of children) were most frequently prescribed for a long-term control of asthma symptoms in China. In Russia, the rate of commonly prescribed long-term relievers ranged as follows: inhaled corticosteroids -54.1%, cromones-19.6%, inhaled corticosteroids in combination with long-acting beta-2-agonists -15.4%. The drug prescribing patterns for bronchial asthma management in pediatric patients of Russia and China conformed to the modern treatment standards. Still, some differences in asthma therapy (relatively short anti-inflammatory therapy courses, unreasonably prescribed cromons in Russia) were found, which required deeper pharmacoepidemiological monitoring in that field.

Keywords: *Commonly prescribed asthma medications in pediatric patients, Mistakes in pediatric asthma management, Asthma medication prescribing in China and Russia.*

Introduction

In recent years, the worldwide incidence of atopic allergic disorders, including bronchial asthma (BA), has sharply increased [1, 3]. This fact is associated with a rapidly increased concentration of various exogenous industrial allergens in the air and side effects of drug use in early childhood [4, 6].

BA is among the most common chronic diseases in pediatric medicine [7, 2, 5], causing a restriction of physical activity in school-age children [8]. Thus, the number of school-age children with BA is three times larger than of those not suffering from this disease [2, 8, 9].For instance, in 2013, children with BA at the age of 5-17 years missed 1.380.000 school days (2.8 days per a child) [9]. Asthma, pneumonia and different injuries are the main causes of pediatric hospitalization in the USA [2, 9]. The world mortality rate due to BA in children varies from 0.0 to 0.7 per 100.000 [10]. The studies show that about 334 million people throughout the world suffer from BA [10, 2]. The asthma prevalence varies over the time and is different in each area, being more common in industrialized countries. Thus, the difference can be striking: up to 13 times higher in certain countries [10, 11, 2]. In different countries the prevalence of this disease generally ranges from 1 to 21% among the adult population [12, 2], whereas about 20% of children at the age from 6 to 7 years suffer the episodes of severe rhonchi and wheezing within a year [13].

One of the countries with high asthma prevalence is Australia, where about 2.7 million people suffer from this disease. This makes 11.2% of the total population [14, 15, 16].Among children aged from 0 to 14 years, about 12.3% of boys and 10.2% of girls suffer from BA [15]. In Spain, the prevalence of BA is about 10% [2]. In the United States, in 2018, this value comprised 7.5% (according to Centers for Disease Control and Prevention), with asthma more common among boys (8.3%) than among girls (5.5%). It was also more typical in children over the age of 5 years (about 8.1%) than in pediatric patients under this age (3.8%).

Besides, asthma prevalence among Spanish-speaking dark-skinned children (15.7%) and children of Puerto Rican origin (9.6%) was higher than in Spanish-speaking Caucasian children (8.2%). It was also higher in children of low-income families (10.8%) compared to those whose family income was more than 250% of the Federal Poverty Level (about 7.3%) [17]. The studies also found that in the United States, the prevalence of pediatric asthma increased from 8.7% to 9.4% within a period between 2001 and 2010, while within a period between 2010 and 2016 it decreased to 8.3% [9].

The 2015 Global Initiative for Asthma (GINA) Guidelines suggested using short-acting beta-2-agonists (SABA) as quick-relief drugs for treating asthma attacks in children, whereas inhaled corticosteroids (ICS) and leukotriene receptor antagonists (LTRA) in combination with ICS were recommended for symptom control management [18, 2]. The combination of ICS and long-acting beta-2-agonists (LABA) was removed from the 2015 GINA Guidelines due to the lack of solid evidence base of this regimen's safety in children [2]. Regardless of a large number of recently produced modern and effective asthma relievers and controllers along with a large number of issued guidelines for the mentioned disease treatment, the pediatric asthma control is still poor [19, 14, 2]. This is due to the fact that a considerable part of children do not receive a sufficiently effective asthma treatment in accordance with modern world standards. Besides, BA therapy can differ considerably in various countries [20, 21].

In real practice, the compliance with asthma treatment is quite low and varies from 30% to 70% [2]. In addition, such factors as the socioeconomic status of the family, the parents' personal beliefs, peculiarities of the child, and the treatment regimen greatly influence the situation [22, 20]. Uncontrolled BA affects a child's quality of life and leads not only to considerable economic costs of certain families, but also of the society as a whole. Thus, in 2012, the average costs for asthma management in the United States amounted to $983 per a child for each taxpayer [23]. It is absolutely obvious that the correctly prescribed treatment pattern plays a key role in a successful control of BA symptoms.

Therefore, the monitoring studies aimed to facilitate rational medication use for asthma treatment are especially relevant. Unfortunately, such studies were mainly conducted among adult patients, while pediatric data are rather limited. That is why the research in this field is of great importance, especially since the knowledge of appropriate drug use and children's compliance with asthma treatment will help improve the process of asthma management in pediatric patients. *The study aims to analyze* medication prescription patterns for asthma treatment in pediatric outpatient care of Russia and China, as well as evaluate the prescribed therapy conformity with the modern international standards on asthma treatment.

Materials and Methods

Table 1: Comparative statistics on the prescribing frequency of the major drug groups for asthma management in pediatric patients of China and Russia

Drug group	Studied groups				X^2	p
	Group 1, Chinese pediatric patients (n=393)		Group 2, Russian pediatric patients (n=327)			
	Frequency	Percentage	Frequency	Percentage		
SABA	329	83.7	257	78.6	2.09	0.149
ICS	256	65.1	177	54.1	7.965	0.005*
LABA	9	2.3	29	8.9	14.445#	<0.001*
LABA + ICS	32	8.1	50	15.3	9.372	0.003*
LTRA	73	18.6	10	3.1	41.483	<0.001*
Cromones	5	1.3	64	19.6	67.756#	<0.001*
OCS	38	9.6	27	8.3	3.447	0.064
Xanthines	-	-	26	8	30.526	<0.001*

Note: * – the difference is statistically significant between the comparison groups (p <0.05); # – $\chi 2$ criterion was calculated with Yates' correction
SABA – short-acting beta-2-agonists; ICS -inhaled corticosteroids; LABA-long-acting beta-2-agonists; LTRA-leukotriene receptor antagonists

There were also some differences in the frequency of LABA and LABA/ICS combination use: they were prescribed considerably more frequently in Russian pediatric patients (p <0.05) than in Chinese ones. Regarding LTRA use, the tendency was quite opposite: drugs of this group were prescribed with a statistically significant higher frequency (p <0.05) in China (in 18.6% of cases) than in Russia (only in 3.1% of cases). Still, in Russia the prescribing frequency of cromons (p <0.05) and xanthines (p <0.05) was quite high.

For instance, cromons in Russia were prescribed in 19.6% of cases, while in China they were only prescribed for 1.3% of children. At the same time, no xanthine prescriptions in medical histories of Chinese pediatric patients were found. In Russia, the mentioned drug groups were prescribed in 8% of cases. Regarding the use of oral corticosteroids (OCS), there was no statistically significant intergroup difference in the prescribing frequency of these medications (p> 0.05). The analysis of the age structure of the main asthma medication prescriptions (Fig. 1, 2) showed a gradual increase of ICS prescribing with age in both comparison groups. It was also found that girls have been prescribed ICS more often than boys, although no statistically significant differences have been found (p> 0.05). Among Chinese patients, there was a tendency to have a decreased proportion of LTRA prescriptions with age (p> 0.05).

The study of the age prescription structure of the main asthma drug groups in pediatric patients of Russia showed that cromons were considerably more often prescribed (p <0.05) in children aged between 0 and 4 years in comparison with elder age categories.

In pediatric care of Russia, there was also a tendency (p> 0.05) to increase the prescribing

frequency of xanthines and OCS with age.

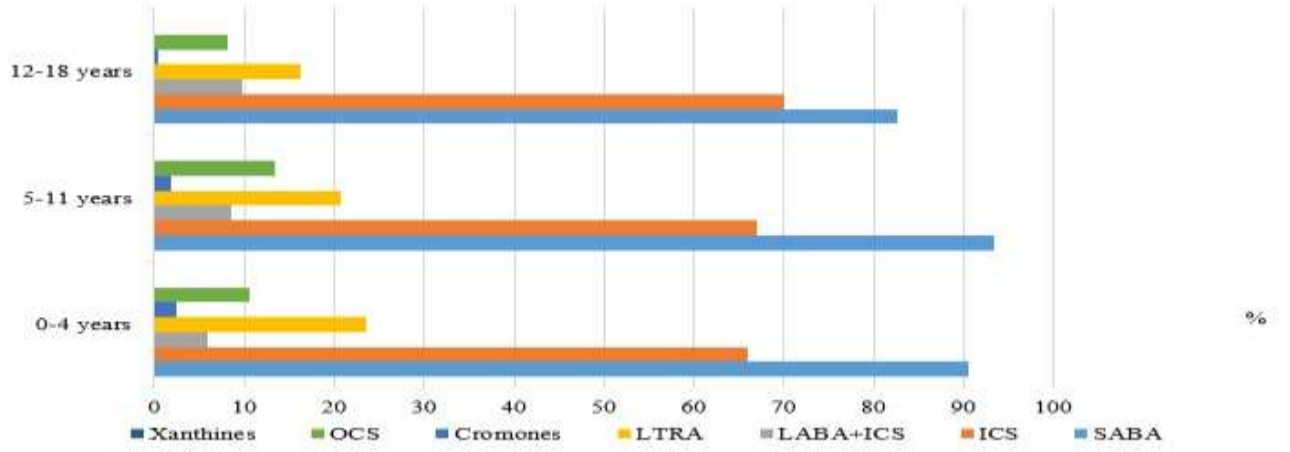

Figure 1: Age distribution of the main drug groups frequently prescribed for asthma in pediatric patients of China, %
Note: SABA – short-acting beta-2-agonists; ICS – inhaled corticosteroids; LABA – long-acting beta-2-agonists; LTRA – leukotriene receptor antagonists.

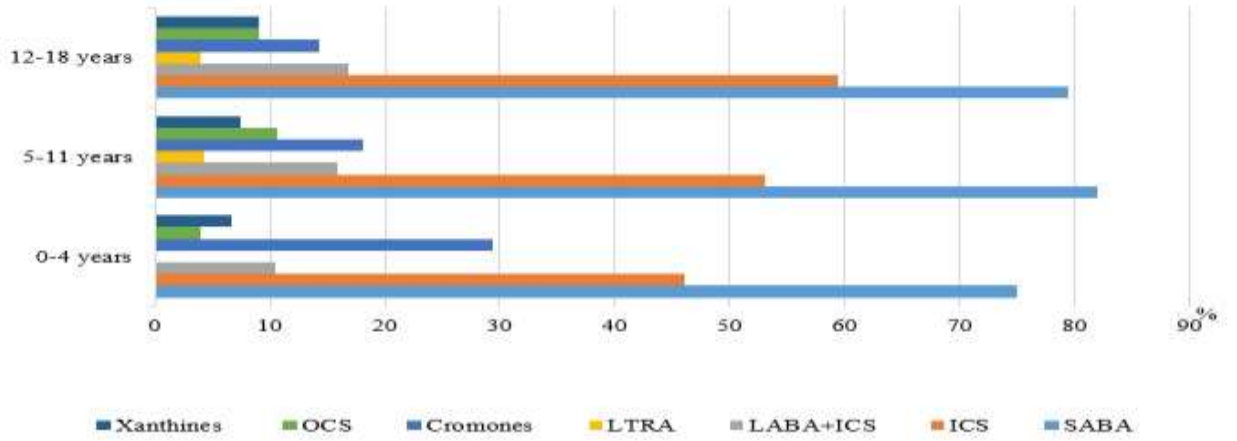

Figure 2: Age distribution of the main drug groups frequently prescribed for asthma in pediatric patients of Russia, %

Note: SABA – short-acting beta-2-agonists; ICS – inhaled corticosteroids; LABA – long-acting beta-2-agonists; LTRA – leukotriene receptor antagonists.

Discussion

The analysis of the main frequently prescribed medications for asthma in pediatric patients of Russia and China enabled the clinicians to claim that the pediatric asthma therapy patterns in the mentioned countries generally met the international asthma treatment requirements [2, 18, 24].However, some considerable differences and disadvantages of prescribed regimens were found, which must be corrected for a proper BA control. Thus, a widespread use of cromons in Russian pediatric care was noticed. These drugs are associated with suppressing the early and late-stage asthma by blocking mast cell degranulation, which results in reduced release of histamine, bradykinin, prostaglandins, leukotrienes, slow-reacting substance, etc.

Therefore, the allergen-induced bronchospasm is controlled, as well as that induced by another trigger [25]. The conducted study showed that in Russia cromons were predominantly prescribed in patients of early childhood (from birth until the age of 4). As the children aged, the prescribing frequency of the mentioned drug group decreased considerably ($p < 0.05$). One of the problems caused by cromons intake was the prescription to take them 4 times a day. That was rather inconvenient for the pediatric patients, which resulted in a poor compliance with treatment. Due to this, cromons were often less frequently prescribed than the standards required [2, 25]. Thus, only 41 (64.1%) out of 64 children took the mentioned drugs 4 times a day. Moreover, cromons were prescribed to children with a moderate persistent state of disease, which was

not completely correct, since the drugs of that pharmacological class were considerably less effective than ICS were [26, 2]. Compared with China, ICS in Russia were statistically less frequently prescribed ($p < 0.05$). In compliance with international standards [18, 2], ICS constitute the main drug group, which should be used in BA therapy as long-term and stable controllers, since currently this class of asthma drugs is the most statistically effective in pediatric asthma treatment [27, 26, 18, 2, 28]. Both cromons and ICS were characterized by short treatment courses of less than 6 months, and only 56% of the children, receiving the mentioned medication therapy, took them regularly. Meanwhile, in China, some children were prescribed ICS treatment and 85.5% of them took corticosteroids regularly, which was statistically higher compared to Russia ($p < 0.05$).

Regarding the OCS use, the study showed that there was no considerable difference in their prescribing frequency in pediatric patients of Russia and China.Thus, there was no statistically significant intergroup difference in the frequency of OCS prescribing ($p > 0.05$). They found that in comparison with Chinese pediatric patients, there was a statistically ($p < 0.05$) greater number of Russian children, who were prescribed LABA or LABA/ICS therapy. The combination of LABA and ICS helps achieve and maintain asthma symptom control [28] but there is no evidence base regarding the safety of the treatment regimen for pediatric patients, especially in early childhood. Therefore, the mentioned drug group combination was excluded from the 2015 GINA Guidelines [2].

The analysis of the medication prescription patterns for pediatric asthma in the studied countries showed that in China, there was a statistically higher prescribing frequency ($p < 0.05$) of LTRA, blocking Cysteinyl leukotriene receptors **(**CYSLTR1) of airways, and inhibiting the leukotriene effect and bronchoconstriction in patients with BA [29]. LTRA therapy can be prescribed as ICS alternative in managing the intermittent asthma or in combination with ICS due to insufficient response to ICS monotherapy [29, 18, 2].The high efficiency of LTRA for asthma treatment is clinically proven [29, 30, 31, 32].Thus, there was conducted an open multicenter study in Canada, including 328 children with uncontrolled BA. The average age of the children was 6.9±3.4 years. There were 2 comparison groups formed: group 1 (n=76) received montelukast monotherapy, whereas group 2 (n = 252) received montelukast in combination with ICS. In three weeks, 61.3% of children of the 1st group and 52.9% of children of the 2nd group gained control over their disease. At the end of treatment (week 12), these values increased up to 75% and 70.9%, respectively [30]. The study found that in Chinese pediatric care, LTRA were commonly prescribed to children of early childhood (0-4 years) (Fig. 1), and decreased with age. This can be explained by the fact that children of early childhood often have difficulties using the ICS inhalation devices, while LTRA are highly effective drugs produced in a tablet form. They are more convenient for younger children in use, which provides higher treatment compliance compared to ICS.

The clinicians noticed a relatively widespread use of xanthines in Russian pediatric care Russia. These drugs were prescribed in 8% of cases but no information about the prescribed xanthine therapy in medical histories of Chinese children was found. Xanthines are associated with many side effects such as allergic reactions, tachycardia, hypotension, increased diuresis, lower esophageal sphincter relaxation, headache, hypermotivity, hyperhydrosis, rhabdomyolysis, metabolic acidosis, hypokalemia and hyperglycemia [33]. Due to this, the use of the mentioned drugs in pediatric asthma patients of Russia remains unclear. Furthermore, there was a rare prescribing of modern and safer drug group of LTRA.

It was also noticed that in Russia xanthines were sometimes used as quick-relief drugs for treating asthma attacks. Moreover, they were underdosed, which could not provide the necessary broncholytic action. When analyzing the similar studies conducted in other countries, one could note rather different trends in medication prescribing for asthma management, which was obviously specified by the existing standard prescribing patterns, as well as by the socio-economic situation of a certain country. There was conducted a population-based cohort retrospective study in the Netherlands, analyzing medical records (kept in the primary health care database) of 14303 children with BA (35181 person-years of follow-up) aged from 5 to 18 years within a period between 2000 and 2012. It was found that children were commonly prescribed SABA (40 children per 100 person-years of follow-up) and ICS therapy (32 children per 100 person-years of follow-up) [20]. In South Korea, a retrospective study was conducted that analyzed insurance benefit claims (n = 1590228, age from 0 to 18 years) within a period between 2010 and 2014. It was found that the number of pediatric asthma patients increased from 1.172.807 (in 2010) up to 1.590.228 (in 2014). Sixty percent of the outpatient children were prescribed LTRA, while only 15% of them were prescribed ICS or a combination of ICS and SABA [34]. A retrospective observational study was conducted in the UK (n = 11641, age from 0 to 18 years: 33% - 0-4 years, 41% - 5-11 years, 22% - 12-18 years), analyzing the primary medical database within a period between 2001 and 2006. The rate of the following medication prescriptions ranged as follows: SABA - 82.3%-91.4%, ICS - 50.2-62.5%, OCS - 6.5-16%, LABA - 1.6-5.2%, ICS/LABA combination - 2.2-11.6%, LTRA - 3.8-8, 4%, cromons - 0.1-0.2% [35].

The results of the study were similar to the findings of the conducted comparative analysis. A significant large-scale retrospective study was conducted in the United States, analyzing prescribing regimens for asthma management in children aged 6 to 11 years. The data of patients registered in the PharMetrics database within the period between June 1, 1995 and September 30, 2008 were studied. The cohort of pediatric patients with BA was 659.169 children, while 34.950 (5%) of them had severe asthma. The studied subgroup included 374.068 children (56.7% of the total cohort of pediatric patients with BA) aged 6 to 11 years.

The frequency rate of prescribed medication groups in children with mild and severe asthma ranged as follows: SABA -53% and 92%, OCS - 23% and 64%, LTRA -17% and 49%, ICS -15% and 80%, ICS/LABA combination -10 % and 22%, respectively. In addition, it was found that a considerable part of children with BA did not receive any drugs, and compliance with the recommendations of the children receiving asthma therapy also raised doubts [36].

Findings

The analysis of medication prescribing patterns for bronchial asthma management in children revealed differences in the prescribing frequency of certain drug groups for asthma in pediatric care of Russia and China. Short-acting beta-2-agonists were most often prescribed in both countries (in 83.7% of children in China and 78.6% in Russia ($p > 0.05$) as the main relievers for asthma attacks. Inhaled corticosteroids (in 65.1% of cases) and leukotriene receptor antagonists (in 18.6% of children) were most frequently prescribed for a long-term control of asthma symptoms in China. In Russia, the rate of commonly prescribed long-term relievers ranged as follows: inhaled corticosteroids -54.1%, cromones -19.6%, inhaled corticosteroids in combination with long-acting beta-2-agonists - 15.4%. A statistically significant intergroup difference in the prescribing frequency of the mentioned medications was found.

In general, the frequency prescribing patterns for bronchial asthma management in pediatric patients of Russia and China conform to the modern treatment standards. However, a number of differences was found (frequent unreasonable use of cromones in Russia, omission of leukotriene receptor antagonists use as an alternative to inhaled corticosteroids in managing the intermittent asthma, relatively short courses of anti-inflammatory

therapy), which requires the further detailed pharmacoepidemiological monitoring in this field. This will reduce the number of prescribing errors and increase the compliance with asthma treatment in children.

Perspectives for further research. Study the amounts of medications from the main asthma drug groups most frequently used in Russian and Chinese pediatric care by determining and comparing the daily doses of these drugs in relation to the patient's age and asthma severity.

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