

# Changes in the list of over-the-counter drugs containing biologically active substances of plant origin which are intended to be applied among pediatric patients in Bulgaria

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## Abstract

Over-The-Counter (OTC) drugs constitute a large category found in pharmacies. They are intended to be applied among adult patients and infants as well. They are also used for prophylaxis.

The number of OTC drugs containing biologically active substances (BAS) of plant origin which are intended to be applied among children is insignificant. The changes in the list of OTC medicines which are applied among children mainly affect products influencing cold and flu symptoms. These medicines often contain decongestants which are considered to be the main reason for the emergence of a number of unwanted drug reactions. In addition, the list of OTC drugs has been supplemented with new medicines, most of which contain the same BAS of plant origin, but the product has been produced by a different manufacturer.

## Keywords

over-the-counter drugs, pediatric patients, children, herbal medicine

## Introduction

Over-the-counter (OTC) drugs are widely accessible in pharmacies, drugstores and also on various Internet websites. In some pharmacies, these medicines are placed in the free-access area. The specified conditions and other similar conditions serve as a prerequisite for their increased use.

The category of a given medicine, be it a medicine prescribed by a doctor or an over-the-counter medicine, is determined by its safety and effectiveness profile (Khan et al. 2013). The main features that OTC drugs shall have been the following: proven safety; convenient use; the number of the dose units shall be conformed with the duration of the intake; the information contained in the leaflet shall be accurate and complete.

The U.S. Food and Drug Administration, the OTC/Nonprescription drugs department, the pediatric and maternity health unit and the pediatric therapy department have set the following criteria for the OTC products: they can be used by consumers for self-treatment in an appropriate manner; no medical specialist is required for their safe and effective use; they have a low abuse rate (American Academy of Pediatrics 2020).

In Bulgaria, the Medicinal Products in Human Medicine Act is the normative document regulating the regime of the over-the-counter medicines, which has been stipulated in Chapter Seven entitled “Classification of medicinal products” (Ministry of Health Republic of Bulgaria 2023).

In addition, these medicines are easily accessible and the patients/parents themselves become active participants when choosing a medicine and the treatment (Cooper 2013).

Over-the-counter drugs are usually used in cases of non-serious up to medium conditions and also before the provision of medical aid (Siopen et al. 2013).

Over-the-counter drugs are used not only for prophylaxis, but also in the treatment of a wide range of conditions such as a headache, cold, musculoskeletal pains, allergies, nicotine addiction, stomach acid and others (Sansgiry et al. 2017; Lebanova et al. 2020; Schifano et al. 2021).

A number of examples have been found in literature which show that an increasing number of parents give OTC drugs to their children in case of various diseases (Halim et al. 2010), as the reasons and the factors for this have not been completely established (Andritsou et al. 2017).

A conducted study has shown that the most commonly used medicines prescribed by a doctor to be used among children aged 0–18 years are analgesics, antibiotics, dermatological, respiratory and antihistamines.

Some of the over-the-counter drugs are analgesics and also those medicines used to relieve cold symptoms (Kesti et al. 2023).

## Aim

Our study analyzes the aspect of the changes that have occurred for a period of three years in the list of the OTC drugs intended to be applied among children.

## Materials and methods

### Documentary method

A documentary analysis of the list of over-the-counter medicines in the Republic of Bulgaria dated 23<sup>rd</sup> August 2023. The list has been published on the official website of the Bulgarian Drug Agency. We have examined the OTC drugs with reference to the following indicators: active substance content; age differentiation of the pediatric patients; distribution of the registered OTC drugs in terms of indications for use /nosology. Comparison of the obtained data with those from the list of OTC drugs dated 25<sup>th</sup> January 2020.

## Statistical method

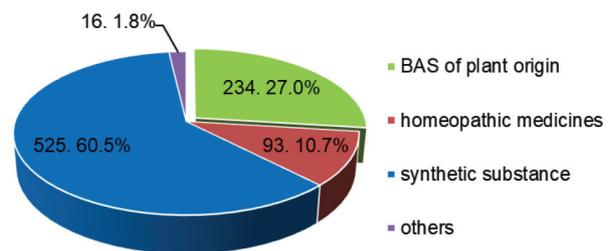
Statistical data processing was performed with IBM SPSS v.23. The variables with non-normal distribution were compared with the Kruskal-Wallis test and the Mann-Whitney test. The relationship between categorical variables in cross tables was analyzed using  $\chi^2$  test.

For the significance level of the null hypothesis, we assumed at  $P < 0.05$  at 95% confidence interval.

MS Excel 2016 was used for graphical representation of the results.

## Results

The list of over-the-counter drugs is accessible on the official website of the Bulgarian Drug Agency. It is periodically updated. Based on official data, 1077 over-the-counter drugs are included in the list as on 23<sup>rd</sup> August 2023. As a result of the conducted analysis of 1077 OTC drugs, we have established that 868 (80.6%) can be applied among pediatric patients, of which 234 drugs (27%) contain biologically active substance/s of plant origin (individually, in combination with another one, in combination with a synthetic substance or a derivative + a synthetic substance), 93 (10.7%) are homeopathic medicines, 525 (60.5%) are synthetic substance (Fig. 1).



**Figure 1.** Distribution of the OTC drugs based on the active substance, which are intended to be applied among pediatric patients.

We classified the remaining 16 drugs (1.8%) as others for which the summary of product characteristics (SmPC) contains the following information: “To be carefully applied among children!”, “Children aged 6–12 years shall take half a dose, i.e. one tablet”. We have also included in the group of the others those OTC drugs with reference to which the following has been stated: “The use of Drotaverin among children has not been assessed in clinical surveys”, which has been written about NO-SPA 40 mg tabl, and with reference to DRO-SPAZ 40 mg. tabl, the summary of product characteristic (SmPC) states the following: “The use of Drotaverin has not been assessed in clinical surveys but if it is necessary to use Drotaverin: children aged 12 can be given ...”.

The distribution of non-prescription drugs containing in their composition only BAS from plant raw materials, a combination of BAS from plant raw materials, a derivative or another version of the composition in which BAS of plant origin is present has been shown in Fig. 2.

Compared to the list of OTC drugs as of 25<sup>th</sup> January 2020, the number of registered over-the-counter plant-based drugs administered to children was 198 out of a total of 999 (Petkova and Hadzhieva 2021), or their number has increased by 36 products.

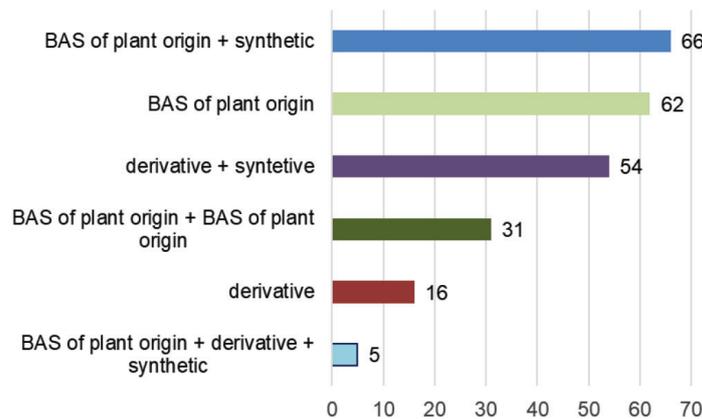
According to the active substance content, the number of OTC drugs containing only a plant component, which are intended for use among pediatric patients in the 2023 list was 62 (26.5%) and in the 2020 list it was 57 (29%), with which we have proven that there is no significant difference regarding these over-the-counter drugs. We have also established that among the studied medicines, there has been an increase in the number of those that mostly contain the same plant active substance (e.g. dry extract of the leaves of *Hedera helix* L., folium), but the product is from a different manufacturer, and also those intended to affect cold and flu symptoms.

In terms of nosology, we have proven that the registered new OTC drugs are intended to be used among children primarily in cases of a cold, presented in Fig. 3. For the purposes of statistical analysis, we have divided the indica-

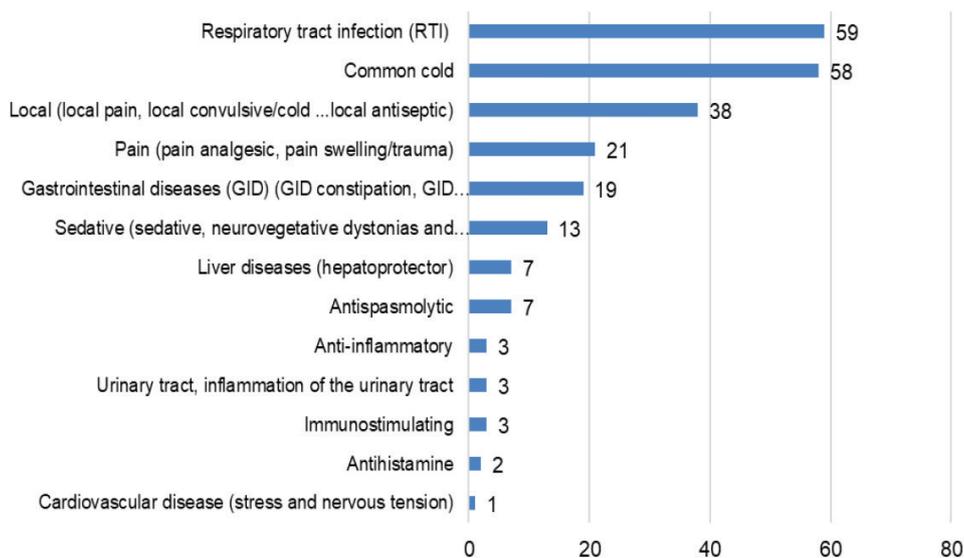
tions into 13 groups as follows: common cold; respiratory tract (RT) (incl. RT cough, RT throat, RT rhinitis/sinusitis, RT acute infections/bronchitis, RT nose/nasal congestion); pain (pain analgesic, pain swelling/trauma); gastrointestinal tract (GIT) (GIT constipation, GIT antacid/carminative, GIT antacid, GIT colic/flatulence, GIT biliary-hepatic dysfunction); sedative (sedative, neurovegetative dystonias and kinetoses); immunostimulant; antispasmodic; urinary tract, inflammation of the urinary tract; liver diseases (hepatoprotector); cardiovascular disease (stress and nervous tension); antihistamine; anti-inflammatory; local (local pain, local convulsive/cold, local pain/edema/trauma, local epithelializing/scarring, local wound healing, local neurodermatitis/urticaria/antihistamine, local antiseptic).

We have examined the number of OTC drugs containing BAS of plant origin, a derivative or and in a combined composition that are used for cold symptoms among children based on their age (Fig. 4).

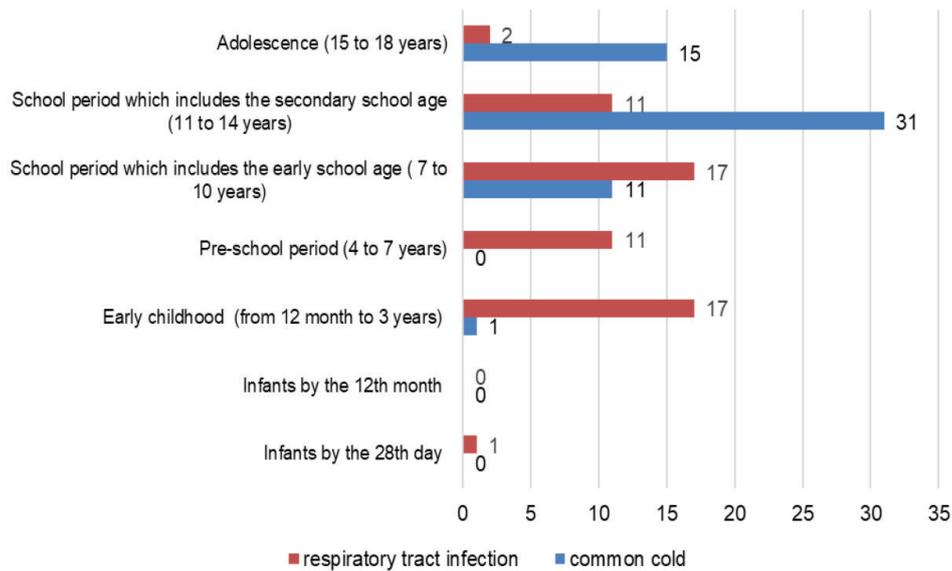
We have established that there was no significant difference in the number of OTC medicines containing a



**Figure 2.** OTC drugs containing BAS of plant origin, a derivative or and in a combined composition applied among children aged 0+ - 18 years.



**Figure 3.** OTC drugs containing BAS of plant origin, a derivative or and in a combined composition applied among children with various indications.



**Figure 4.** OTC drugs with BAS of plant origin applied among children with a cold and flu.

plant component that could be administered in the infancy-early childhood period (0–3 years), the number being as follows: 25 medicines for 2023 and 21 for the year 2020.

In addition, beyond the scope of our study, we have established that in the list of medicinal products without a doctor's prescription in Bulgaria as of 23.08.2023, updated on 20.12.23, there are medicinal products that lack the summary of product characteristics (SmPC) in the register of the official page of the Bulgarian Drug Agency. Also, one medicinal product was entered twice, and in three cases, the order of entry was not respected according to the chronology of the Latin alphabet.

## Discussion

Our study has shown that for the year 2020, and also as of August 2023, in the list of over-the-counter drugs used among children, the largest is the share of those intended to affect the symptoms of the common cold and flu. We could define as a positive change the addition of medicines for flu and cold to the OTC list, since children are most often ill with colds and coughs.

Substances of different structure and origin are present in the composition of non-prescription drugs. Herbal medicines have always been the focus of the pharmaceutical industry for a number of reasons. Traditional medicines are generally known to be harmless, more effective with minimal side effects, and easily metabolized and absorbed by the body. Synthetic drugs, on the one hand, provide quick relief, but have many adverse effects and are also more expensive, making them financially unaffordable (Nasim et al. 2022).

Examining the composition of OTC drugs used for the symptomatic treatment of children with flu and colds, we have established that a number of them contain a decongestant and antihistamine (Sharfstein and Serwint 2007).

It should be noted that a number of studies have reported adverse effects following the use of the decongestant and

antihistamine combination in children (Isbister et al. 2012; Şahin and Gülen 2015; De Sutter et al. 2022). Antihistamines (such as pheniramine maleate), decongestants (pseudoephedrine, phenylephrine hydrochloride, dimethidine) contained in OTC drugs lead to an increase in the frequency of adverse reactions (Lokker et al. 2009), therefore, the application among children under 6 years of age is limited and should be done only under medical supervision. The use of over-the-counter cough and cold drugs among pediatric patients is widespread in the United States, although patterns of use are unknown, leading to adverse reactions and death of children (Wingert et al. 2007; Vernacchio et al. 2008). Also, the U.S. Food and Drug Administration (FDA) and the Healthcare Consumers' Association recommend that these drugs not be given to children under 4 years of age due to the potential risk (Briars 2009; Shefrin and Goldman 2009).

At the end of 2023, the Medicines Safety Committee (PRAC) of the European Medicines Agency (EMA) made new recommendations for drugs containing pseudoephedrine (European Medicines Agency 2023). Due to the risk of toxic manifestations resulting from the use of OTC drugs containing the combination of decongestant + antihistamine, paracetamol is given to children since birth to affect the symptoms of pain, fever and cold (Meremikwu and Oyo-Ita 2002; Kanabar 2017).

## Conclusion

OTC drugs given to children to treat cold and flu symptoms are widely available on the pharmaceutical market in Bulgaria and their number has grown over the past three years. Most of these OTC products contain substances such as pseudoephedrine and, according to the short description of these medicines, they should not be given to children under 6 years of age.

The challenge for the pharmaceutical manufacturers is to find mechanisms to implement OTC drugs that con-

tain BAS of plant origin with an anti-inflammatory and antiviral activity so that they can be administered from an early age.

Through our research, we would like to draw the attention of the responsible institutions to correcting certain omissions in the Register of the short descriptions of medicinal products authorized for use, as well as in the list of OTC products which are available on the official page of the Bulgarian Drug Agency.

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## Conflict of interest

This research has no conflict of interest.

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