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Age-related off-label use of nasal corticosteroids for allergies is relatively common in Finnish children with asthma

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Running title: Off-label nasal corticosteroids and asthma

ABSTRACT (200 words)

Aim: Allergies can worsen asthma symptoms and we used national data to identify allergy medication prescribed for Finnish children and adolescents who used asthma medication.

Methods: Register data were available for 13,435 Finnish children aged 0-17 who were entitled to special reimbursement for asthma medication during 2006-2009. Allergy medication purchases were individually analysed two years before and two years after the entitlement for asthma medication reimbursement was granted.

Results: Two-thirds (66.5%) of the children had used at least one allergy medication during the four-year follow up, with an average of five purchases. Most (91%) of the allergy medication purchased was systemic antihistamines and half (50%) was nasal corticosteroids. In all, 8% of the allergy medication and 22% of the nasal corticosteroids were classified as off-label purchases based on the child's age. Paediatric allergologists and paediatricians prescribed 59% of the allergy medication and 76% of the off-label nasal corticoids.

Conclusion: Most asthmatic children and adolescents used allergy medication. Nasal corticosteroids were the commonly prescribed off-label item and the prescribers were mainly specialists in paediatric allergology or paediatrics. Official dosage instructions and more specific clinical guidelines are needed to support appropriate prescribing of nasal corticosteroids for young children.

Keywords: allergy, asthma, child, off-label drug use, register study

KEY NOTES (70 words)

- Allergies can worsen asthma and we used national data to identify individuals prescribed allergy medication, based on 13,435 Finnish children aged 0-17 who were entitled to special reimbursement for asthma medication.
- Two-thirds of the asthmatic cohort used allergy medication and nasal corticosteroids were the most commonly prescribed off-label item.
- Official dosage instructions and more specific clinical guidelines are needed to ensure the appropriate prescribing of nasal corticosteroids for young children.

INTRODUCTION

Allergies and asthma often coexist in the same patient (1,2). Approximately 60–70% of asthmatic children have allergic rhinitis or nasal symptoms (3,4) and over half (56%) of those with both asthma and allergic rhinitis also have a third allergic disease (1). Atopic eczema and allergic rhinitis often precede the onset of asthma and increase the risk of developing asthma (5,6). It has also been suggested that allergic rhinitis and asthma are manifestations of the same disease (7).

Undertreatment of allergic rhinitis can worsen asthma symptoms (7). In addition, a number of studies have indicated that intranasal corticosteroids may reduce asthma symptoms in some patients (7,8). Moreover, the treatment of allergic rhinitis has been shown to reduce asthma-related hospitalisation and emergency department visits (8). The international Allergic Rhinitis and its Impact on the Asthma (ARIA) guidelines were originally developed in 2001 in collaboration with the World Health Organization and were most recently updated in 2010. They state that the coexistence of asthma and allergic rhinitis should be considered when treating these diseases and that nasal corticosteroids and oral non-sedating antihistamines should be the primary choice for treating allergic rhinitis in children (9). Another study has stated that non-sedating antihistamines should be the primary choice for paediatric urticaria (10). According to a 2014 review, allergy medication is also one of the most prescribed off-label drugs for children (11) and this can be considered problematic because the safety and efficacy of these medicines have not been demonstrated in children.

Despite the frequency and coexistence of allergic diseases, only a few studies have examined the use of allergy medication in asthmatic children and adolescents (1-

4,12,13). Moreover, none of these studies reported the use of allergy medication in children under three years of age. The aim of this register-based study was to assess the prescribing patterns of allergy medication, including age-related off-label use, in Finnish children and adolescents diagnosed with asthma.

METHODS

Study population

Our study population comprised all individuals aged 0–17 years who were entitled to special reimbursement for asthma medication for the first time between 1 January 2006 and 31 December 2009. We extracted the details of any allergy medication purchased for each individual studied over a four-year period, namely two years before and two years after they were entitled to special reimbursement for asthma medication.

Registry data

This study was based on the following three nationwide registers that are maintained by the Social Insurance Institution of Finland: the Prescription Register, the Special Refund Entitlement Register and the Health Care Personnel Register. The Prescription Register contains complete data on reimbursed drug purchases by the Finnish primary care and hospital outpatient population, as every resident in the country is covered by the national health insurance scheme (14,15). A previous study showed that it is highly appropriate to use a prescription database for a long-term follow-up study like this one (16).

In Finland, the Social Insurance Institution reimburses some of the costs of drugs that are prescribed (17). The reimbursement system comprises three categories: the Basic

Refund Category (40% reimbursement), the Lower Special Refund Category (65%) and the Higher Special Refund Category (100%). In the Higher Special Refund Category (100%) the patient still has to pay a non-reimbursable sum of 4.50 Euros for each drug purchased. Asthma belongs to the Lower Special Refund Category, together with other chronic and serious diseases like coronary heart disease and qualifies for 65% reimbursement. Once the patient's payments reach the annual maximum limit, which was 610 Euros in 2014, the patient then pays a fixed contribution of 2.50 Euros for each reimbursable drug per purchase for the rest of the year.

To be entitled to special reimbursement and included in the Special Refund Entitlement Register, a person's condition must meet explicit medical criteria and a medical certificate must be submitted to the Social Insurance Institution. The following International Statistical Classification of Diseases and Related Health Problems - 10th Revision asthma codes were used to detect the study participants from the Special Reimbursement Register: J45, J45.0, J45.1, J45.6, J45.8 and J45.9.

The details of the allergy medication that were purchased were collected for the present study from the Prescription Register for two years either side of the first entitlement to special reimbursement for asthma medication. The data included the name and strength of the preparation, the code for the Anatomical Therapeutic Chemical group, the dispensing date and the number of units or packages that were dispensed. The allergy medication purchases were detected based on the following Anatomical Therapeutic Chemical Classification System codes: R06 systemic antihistamines, R01AC nasal antihistamines, R01AD nasal corticosteroids. In addition, the gender and date of birth for each study participant was collected from the Prescription Register. The date when

the patient was first entitled to special reimbursement for asthma medication was drawn from the Special Refund Entitlement Register.

Ethical considerations

The Social Insurance Institution replaced the identity numbers of study participants and physicians with study identification codes before the data were provided to the research team. Given that only de-identified, register-based data were used and the study participants were not contacted, the study did not require the approval of the ethics committee, according to Finnish law.

Statistical analysis

The study participants were categorised into four age groups for the analyses, namely 0–2, 3–5, 6–11 and 12–17 years, based on their age at the date when they first became entitled to special reimbursement. The asthmatic children were categorised as either users of allergy medication or non users and the users had at least one allergy medication purchase during the four-year periods, two years either side of the first special reimbursement. One purchase comprised one or more packages of a drug bought at the same time. The maximum amount of reimbursed drugs per purchase was three months' supply. The average number of defined daily doses of allergy medication was separately calculated for each study year, to observe allergy medication use before and after the entitlement to special reimbursement.

To study seasonal variations, the four seasons were classified as spring (March-May), summer (June-August), autumn (September-November) and winter (December-February). The physicians were categorised into four groups: 1) paediatric

allergologists, 2) paediatricians, 3) ear, nose and throat specialists, pulmonary disease specialists and other allergologists and 4) physicians with some other or no speciality.

The drug was classified as off-label if the user's age at the time of the purchase was under the authorised age specified in the approved summary of product characteristics (18). Other forms of off-label use, like under dosing, overdosing and the frequency of administration and indication, could not be analysed due to lack of data.

The results are presented in percentages and means with standard deviations (SD) or 95% confidence intervals (95% CIs). All statistical analyses were carried out with SPSS, version 24.0 (SPSS Inc, Illinois, USA).

RESULTS

A total of 13,435 children and adolescents aged up to 17 years received special reimbursement for asthma medication for the first time between 2006 and 2009. At the time of this first entitlement, the mean age of these children and adolescents was 6.3 \pm 4.5 years and the majority were males (59.6%).

Purchases of allergy medication

A total of 8,940 (66.5%) asthmatic children and adolescents had used allergy medication during their individual four-year period, namely two years before and after their first special reimbursement for asthma medication (Table 1). The users were slightly older than the non users (6.9 years \pm 4.5 years versus 5.0 years \pm 4.4 years). The allergy medication users had an average of 5.0 (95% CI 4.9–5.1) purchases during their own individual four-year periods. There was no difference in the mean number of allergy medication purchases for boys and girls (5.1 versus 4.9) (Table 1). However, there was a slight difference between boys and girls aged 6–11, with a mean of 6.3 purchases for boys versus 5.5 for girls. Overall, the mean number of the purchases increased with age. The majority (67.3%) of the allergy medication users had 1–5 allergy medication purchases. The proportions of those with 6–10, 11–20 and over 20 purchases were 21.2%, 9.7% and 1.7%, respectively. The highest number of allergy medication purchases for a single individual during a four-year period was 57.

During the subjects' four-year follow-up periods the users of allergy medication had a total of 44,868 allergy medication purchases and these purchases consisted of 15 different drug ingredients (Table 2). Systemic antihistamines were more commonly used than nasal preparations, by 90.9% versus 52.8% of the allergy medication users

and 60.5% versus 35.1% of the whole study population. The most commonly purchased systemic antihistamines were desloratadine, cetirizine and levocetirizine and for nasal corticosteroids they were mometasone, fluticasone propionate and fluticasone furoate. Nasal antihistamines were rarely purchased.

Most of the study participants (41.8%) had used both systemic antihistamines and nasal corticosteroids during their individual four-year period and 9.1% had only used nasal preparations. In addition, 2.3% had made at least one purchase in all three drug groups: systemic antihistamines, nasal antihistamines and nasal corticosteroids.

Systemic antihistamines were used more than nasal preparations when they were observed in terms of the average number of defined daily doses per year per purchaser (Table 3). Over the four year periods for each subject, the average number of defined daily doses per year increased for both systemic antihistamines and nasal corticosteroids. Although desloratadine was the most commonly purchased systemic antihistamine, the consumption of desloratadine in terms of defined daily doses was considerably lower every subsequent year than the consumption of other systemic antihistamines.

Most of the allergy medication purchases were made in spring (41.7%) or summer (28.8%). Less than one-third of the purchases were made in the autumn (15.3%) or in winter (14.2%). The allergy medication users had an average of 2.1 purchases in spring, 1.4 in summer, 0.8 in autumn and 0.7 in winter.

Age-related off-label prescribing

Of all the allergy medication purchases, 7.6% were classified as off-label due to the age of the study participants. However, 18.8% of the users had at least one purchase with an off-label prescription during their individual four-year periods. Age-related off-label prescribing was more common in nasal corticosteroids than in systemic antihistamines (Table 2). Over half (57.9%) of the nasal budesonide purchases were classified as off-label, whereas there were no off-label purchases of systemic levocetirizine and nasal sodium cromoglycate.

Prescribers of allergy medication

More than half (59%) of all the allergy medication purchases were prescribed by paediatric allergologists or paediatricians (Figure 1), but these prescribing proportions reduced as the study participants got older.

In addition, almost three-quarters (73%) of the off-label purchases were prescribed by paediatric allergologists or paediatricians (Figure 2). With regard to the specific medication groups, nasal steroids were most likely to be prescribed off-label by paediatricians (57%), and paediatric allergologists (19%), while systemic antihistamines were most likely to be prescribed by paediatricians (43%) and physicians whose speciality was not related to paediatrics or allergology or who had no speciality (39%).

DISCUSSION

This register-based study assessed allergy medication use in a nationwide cohort of children and adolescents with diagnosed asthma. Two-thirds of the asthmatic children had used allergy medication during their individual four-year follow-up periods, two years either side of their first entitlement to special reimbursement for asthma medication. Allergy medication use in asthmatic children and adolescents has been previously studied in Finland (3), Turkey (4), France (1,13), Europe and Asia (12) and the United States (2). In five of these six studies, the prevalence of allergy medication use was lower (47–58%) than in our study (1-4,13). The higher prevalence rate in our study may have resulted from a longer study period than in previous studies. The prevalence in the study of European and Asian countries was 85% (12). This high rate was probably due to the fact that only patients with concomitant asthma and symptoms suggestive of allergic rhinitis were included in the study.

Almost 42% of the children using allergy medication had used both systemic antihistamines and nasal steroids in this study. The result was consistent with the previous study carried out in Finland, where 41% of children aged 7-15 had used both types of medication (3). In addition, our finding that systemic antihistamines were more commonly used than nasal corticosteroids was in line with previous studies (1-4,12,13). The majority (70.5%) of the allergy medication purchases were made in spring and summer. This finding was consistent with the tree and grass pollen seasons in Finland and also supports the fact that seasonal allergic rhinitis is more common than persistent rhinitis in children (19).

There were an average of five purchases for the allergy medication users and the number of purchases increased with age. The average number of defined daily doses per year per purchaser increased for most drug ingredients over the course of the four-years periods. This may have resulted from physicians taking more notice of allergy treatments for asthmatic children and adolescents or the increased incidence of allergic rhinitis with increasing age (20). Systemic antihistamines were used for longer periods than nasal corticosteroids when observed in defined daily doses. It is possible that physicians wanted to avoid high corticosteroid loads in asthmatic children and therefore preferred systemic antihistamines to nasal corticosteroids.

Approximately 8% of the allergy medication purchases were age-related off-label purchases. Similar findings were found in two previous studies conducted in Europe among children aged 0–17 years (21,22). Based on our results, nasal corticosteroids, in particular, had considerably high off-label rates (22%). Similar results (17%) were reported in a register-based study conducted in the Netherlands (21). In our study, systemic antihistamines were less likely to be prescribed off-label (2%) than in other studies (5-6%) (21,22). This may have been a result of the differences in the authorised ages in the summary of product characteristics (18). In our study, most of the off-label purchases of nasal corticosteroids (76%) were prescribed by paediatric allergologists or paediatricians.

Finland has national Current Care Guidelines for asthma, atopic eczema, food allergies and hyposensitisation, but not for allergic rhinitis. However, physicians use the international ARIA guidelines when treating allergic rhinitis. The latest 2010 revision of the ARIA guidelines only provides conditional recommendations based on moderate

quality evidence on the use of nasal corticosteroids in children (9). The guidelines state that there is still need for further research on the efficacy and safety of nasal corticosteroids in children. In our study, most of the off-label purchases of nasal corticosteroids (76%) were prescribed by paediatric allergologists or paediatricians and were, therefore, concentrated among physicians who probably had the best, and most recent, knowledge of paediatric allergology. Nevertheless, the considerably high rate of off-label prescribing suggests that there is a need to update the official dosing instructions in the respective summary of product characteristics and in the clinical guidelines related to the use of nasal corticosteroids in young children.

The significant strengths of this study are the population-based data and the use of national health registers had previously been demonstrated to be accurate and applicable for research purposes (14,15). The Prescription Register included information on reimbursed prescription drugs in primary care and hospital outpatients in Finland and it lacked recall and selection bias. The asthma diagnoses can be considered reliable because of the explicit criteria that were required to verify the diagnosis by the Social Insurance Institution (17).

Our study also had limitations. Not all allergy drugs were reimbursable and the range of products that were actually reimbursable could have changed over the years. Products with a small package size and over-the-counter status are usually non-reimbursable and were not included in the Prescription Register. In addition, drugs used in institutional settings and ophthalmological preparations for allergies were not included in the data and, therefore, the use of allergy medication may have been underestimated in this study.

Up to 25% of the allergy medication purchased in Finland is sold over the counter (17). However, allergy medication for asthmatic children forms part of the asthma treatment provided by specialists, so the use of over-the-counter allergy medication is not common in this population. On the other hand, there may be a slight overestimation in allergy medication use, because the dispensed drugs may not necessarily have been taken. Age-related off-label use may also have been overestimated in this study. A purchase was classified as off-label even though in some cases the person's age was only a few days under the recommended age. Furthermore, the authorised ages in the statement of product characteristics for the same medication may differ between countries, so comparing studies can be difficult. For example, fluticasone furoate is authorised for use in children aged four years and over in the United States (23), but in Finland and Sweden the lowest authorised ages are six years (18) and 12 years (24), respectively. We did not have any information about the dosages and indications of the medication and this meant that we could not study off-label use in relation to those factors.

A possible source of error in this study was the age group division, because the subject did not necessarily belong to the same age group for the whole study period, as they were allocated to a group based on their age at the date when they first became entitled to special reimbursement. In addition, we could not record two years of purchases before special entitlement if the child was less than two years of age and this means that the results of this age group are not fully comparable with other age groups.

CONCLUSION

This register-based study showed that the majority of asthmatic children and adolescents also used allergy medication and that these were most frequently systemic antihistamines and nasal corticosteroids. Off-label prescribing was most common for nasal corticosteroids, as every fifth prescription (22%) was considered off-label due to the child's age. However, as the prescribers of off-label nasal corticosteroids were mainly physicians who specialised in paediatric allergology or paediatrics, it can be concluded that there is a clear need to update official dosing instructions and produce more specific clinical guidelines to support the appropriate use of nasal corticosteroids in young children.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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Table 1 Proportion of asthmatic children with at least one allergy medication purchase and the mean number of purchases during their individual four-year study period, two years either side of their first entitlement to special reimbursement for asthma medication, broken down by age and gender.

	Boys n=8,004		Girls n=5,431	
	Children with at least one purchase % (n)	Purchases per child¹ mean (95% CI)	Children with at least one purchase % (n)	Purchases per child¹ mean (95% CI)
All ages	66.7 (5,335)	5.1 (5.0–5.2)	66.4 (3,605)	4.9 (4.7–5.1)
0-2 years	48.8 (1,430)	3.0 (2.9–3.2)	49.3 (727)	3.1 (2.9–3.4)
3-5 years	73.1 (1,455)	5.2 (5.0–5.5)	70.1 (900)	4.7 (4.4–5.0)
6-11 years	80.4 (1,774)	6.3 (6.0–6.5)	74.7 (1,160)	5.5 (5.3–5.8)
12-17 years	76.8 (676)	6.2 (5.7–6.6)	73.1 (818)	5.7 (5.4–6.1)

¹ in those who had at least one allergy medication purchase during a four-year period

Table 2 Proportion of asthmatic children for whom allergy medication was purchased and the proportion of allergy medication purchases and off-label purchases during the four-year study periods for each individual study participant

	Children with at least one purchase n=8,940 % (n)	Purchases n=44,868 % (n)	Off-label purchases¹ % (n)	Lowest authorised age² years
Systemic antihistamines	90.9 (8,128)	69.2 (31,054)	1.6 (490)	
Desloratadine	48.8 (4,359)	32.0 (14,374)	0.7 (98)	1
Cetirizine	37.6 (3,357)	20.3 (9,129)	3.9 (356)	2
Levocetirizine	20.5 (1,836)	13.5 (6,062)	0 (0)	2
Loratadine	4.8 (426)	2.6 (1148)	0.5 (6)	2
Ebastine	1.1 (95)	0.6 (255)	7.8 (20)	12
Fexofenadine	0.3 (23)	0.2 (86)	11.6 (10)	12
Nasal preparations	52.8 (4,719)	30.8 (13,814)	21.0 (2,907)	
<i>Nasal antihistamines</i>	4.9 (435)	1.9 (852)	7.4 (63)	
Sodium cromoglycate	3.8 (338)	1.4 (650)	0 (0)	- ³

Levocabastine	1.0 (92)	0.4 (186)	31.7 (59)	4
Azelastine	0.1 (13)	0.04 (16)	25.0 (4)	6
<i>Nasal corticosteroids</i>	50.4 (4,509)	28.9 (12,962)	21.9 (2,844)	
Mometasone	34.1 (3,050)	16.9 (7,561)	22.4 (1,690)	6
Fluticasone propionate	11.9 (1,060)	5.1 (2,295)	12.2 (280)	4
Fluticasone furoate	9.4 (843)	3.8 (1,709)	20.7 (353)	6
Budesonide	2.9 (261)	1.7 (748)	57.9 (433)	6
Triamcinolone	1.7 (153)	0.9 (394)	15.5 (61)	6
Beclometasone	1.6 (142)	0.6 (255)	10.6 (27)	6

¹ Calculated from all purchases of certain drug ingredient

² Lowest authorised age in Finland according to the statement of product characteristics for each drug (20)

³ Lowest authorised age was not given in the statement of product characteristics

Table 3 Average number of defined daily doses (DDD) per year per child with at least one purchase of allergy medication before and after the entitlement to the special reimbursement on asthma drugs.

	DDDs/year/child with at least one purchase			
	Point of entitlement			
	Before entitlement		After entitlement	
	-2 year (366-730 days)	-1 year (1-365 days)	+1 year (0-365 days)	+2 year (366-730 days)
	mean (95% CI)	mean (95% CI)	mean (95% CI)	mean (95% CI)
Systemic antihistamines	62.4 (59.8–65.1)	72.3 (70.1–74.4)	84.6 (82.2–87.0)	92.7 (90.2–95.3)
Desloratadine	27.8 (25.6–29.9)	32.8 (31.0–34.6)	40.4 (38.1–42.7)	47.5 (44.7–50.2)
Cetirizine	67.5 (63.5–71.4)	78.8 (75.7–82.0)	96.0 (92.1–99.8)	104.6 (100.5–108.7)
Levocetirizine	99.7 (92.4–107.0)	113.8 (108.7–118.8)	137.0 (131.3–142.8)	141.6 (136.4–146.9)
Loratadine	93.9 (82.6–105.1)	98.2 (89.5–106.8)	117.9 (107.4–128.5)	127.0 (114.9–139.1)
Ebastine	108.7 (76.7–140.7)	129.4 (100.4–158.4)	144.9 (116.5–173.3)	154.6 (125.1–184.1)
Fexofenadine	66.0 (-0,6–132.6)	130.9 (65.7–196.1)	133.3 (36.1–230.5)	109.2 (49.9–168.4)

Nasal preparations	55.2 (52.6–57.8)	64.0 (61.7–66.3)	69.0 (66.6–71.5)	68.2 (65.8–70.6)
<i>Nasal antihistamines</i>	25.6 (17.4–33.7)	28.8 (23.1–34.5)	24.2 (21.6–26.7)	24.5 (20.7–28.3)
Sodium cromoglycate	21.8 (19.6–23.9)	28.4 (23.4–33.3)	24.4 (21.2–27.6)	24.6 (20.8–28.4)
Levocabastine	41.7 (-2.3–85.7)	30.7 (10.5–50.8)	23.5 (19.2–27.9)	23.8 (11.5–36.0)
Azelastine	-	24.4 (-78.9–127.6)	23.2 (11.4–35.0)	19.0 (12.0–25.9)
<i>Nasal corticosteroids</i>	57.5 (54.9–60.0)	65.5 (63.2–67.8)	71.3 (68.8–73.8)	69.3 (66.9–71.7)
Mometasone	55.7 (52.8–58.6)	64.1 (61.4–66.7)	71.8 (68.6–75.0)	69.9 (66.8–73.0)
Fluticasone propionate	57.5 (52.9–62.1)	60.5 (56.9–64.2)	67.5 (62.7–72.4)	64.0 (59.3–68.8)
Fluticasone furoate	40.0 (-3.0–83.0)	47.4 (41.6–53.1)	54.2 (49.6–58.8)	52.7 (49.4–56.0)
Budesonide	46.3 (33.3–59.2)	57.2 (43.5–70.9)	57.6 (45.8–69.5)	68.5 (55.3–81.8)
Triamcinolone	44.4 (35.7–53.1)	51.0 (41.1–61.0)	64.3 (47.7–80.8)	73.9 (52.2–95.6)
Beclometasone	63.9 (47.6–80.2)	62.9 (52.6–73.2)	62.7 (49.2–76.3)	80.3 (49.7–110.9)

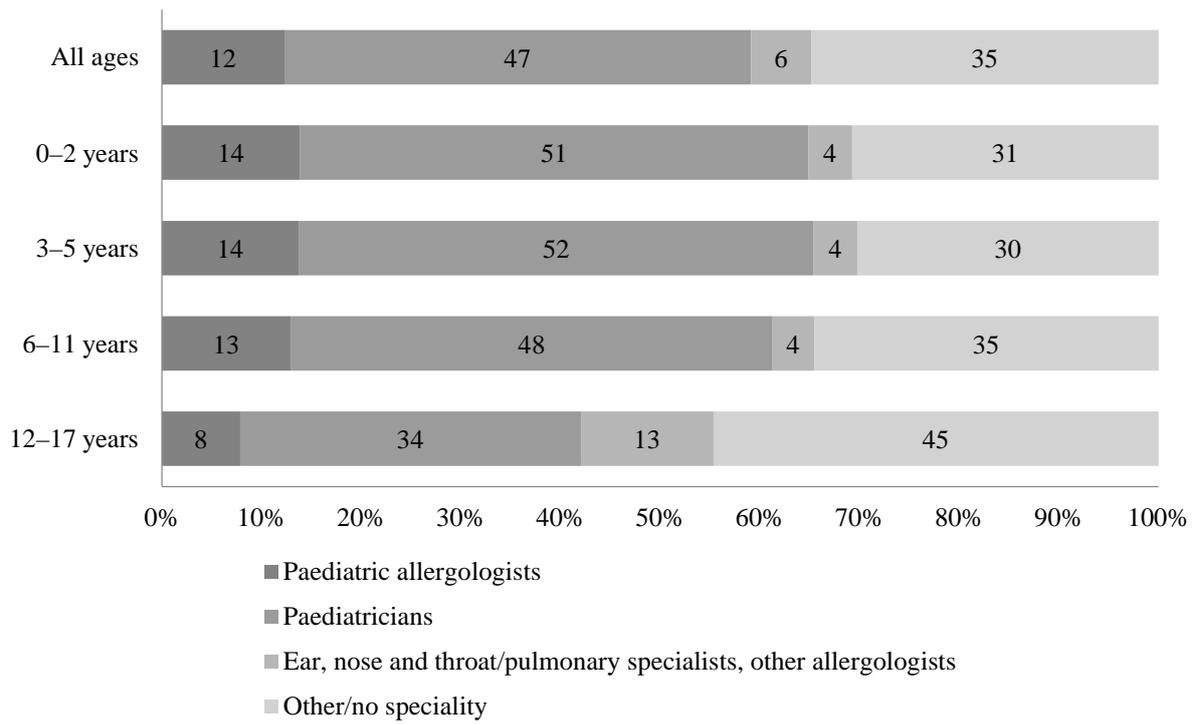


Figure 1 Proportion of allergy medication purchases prescribed by physicians with different specialities according to the age of the children.

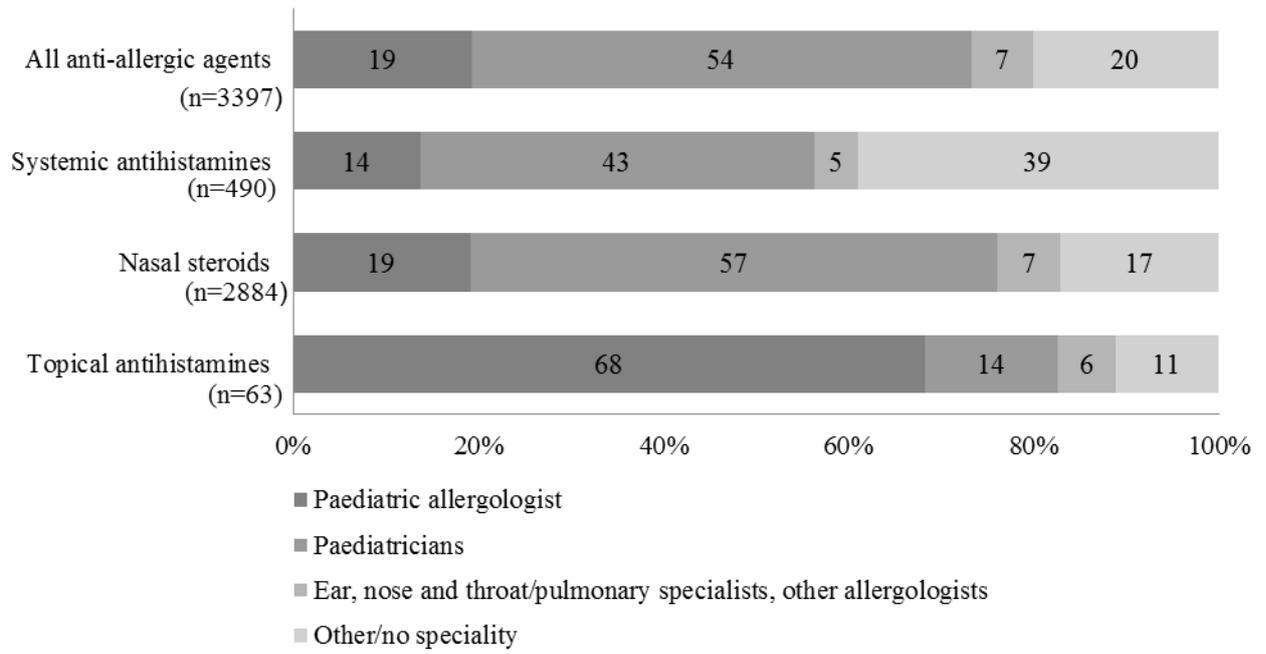


Figure 2 Proportion of off-label purchases prescribed by physicians with different specialities according to the medication group.