

Ten-year prescription trends of asthma medications in the management of childhood wheeze

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ABSTRACT

Asthma is the most common chronic disorder of childhood. The aim of this study was to assess prescription trends of asthma medications to provide a measure to evaluate treatment practices and compliance with established international practice guidelines. A retrospective study of data obtained from outpatient prescription databases (2001–2010) of the University Children's Medical Institute for children aged 0–18 years was performed. The following drugs were included: short-acting beta-agonists (SABAs), long-acting beta-agonists in combination with inhaled corticosteroids (LABA–ICSs), ICS, and leukotriene receptor antagonists. Statistical analysis of prescription trends was performed with linear regression to determine the trends in prescription of controller medications. From 2001 to 2010, the number of patients who were prescribed SABA increased significantly by 72% ($p = 0.016$). The increases in ICS patient numbers and ICS/SABA drug unit ratios were significant only in the school-going (>5 years) age group. There was a trend away from the use of nebulized SABA and ICS, although this was statistically insignificant. LABA–ICS patient numbers decreased significantly by 32.4% ($p = 0.003$), especially in preschoolers (1–5 years). There was a corresponding rise in montelukast patient numbers by 194.6% ($p = 0.009$) and montelukast/SABA ratio by 345.3% ($p = 0.032$) in preschoolers (aged 1–5 years). Montelukast patient numbers, but not the montelukast/SABA ratio, increased in school-going children. The move away from LABA–ICS combination especially in younger children and a tendency toward more montelukast usage is a reflection of practice preferences in accordance with current international guidelines in young children.

(Allergy Asthma Proc 35:e1–e8, 2014; doi: 10.2500/aap.2014.35.3712)

Childhood wheeze is one of the most common clinical disorders encountered in pediatrics. A subset of these children has asthma, a common chronic disease in children. The economic burden of asthma^{1–3} and the impact on the quality of life⁴ are high. Thus, good control of asthma remains an important imperative.

In the last 10 years, there has been greater attention paid to the differences in wheezing between younger and older children. The Global Initiative For Asthma made recommendations against add-on therapy with long-acting β -agonists (LABAs) in children <5 years old in 2009.⁵ The PRACTicing ALLergy guidelines in 2008⁶ allowed for LABAs to be added on from the age of 3 years onward. The European Respiratory Society article on preschool wheeze in 2008⁷ mentioned LABAs briefly without any specific

recommendation for or against their use. Finally, the National Heart, Lung, and Blood Institute's guidelines, based on their Expert Panel Report 3 in 2007,⁸ mentioned LABA as a possible option at step 4 care for children aged 0–4 years. In all of these guidelines, inhaled corticosteroid (ICS) was the first choice of controller therapy, and leukotriene receptor antagonists were mentioned as a viable option for treatment of childhood wheeze.

The use of LABA–ICS combinations have raised controversy. Recent studies have linked monotherapy with LABAs to increases in asthma-related morbidity, deaths, and severe exacerbations.^{9–11} Following the Salmeterol Multicenter Asthma Research Trial, the Food and Drug Administration issued a black box warning on the LABAs in October 2005. The approved age of use for LABA–ICS combinations is restricted; one example is the salmeterol–fluticasone combination, which is approved for use only in those aged ≥ 4 years.

The study of prescription trends over time of the different classes of asthmatic drugs among pediatricians can yield useful information: not only does it reflect current practice and physician preference in prescribing, but it may also be a surrogate marker of current treatment preference for wheeze and asthma.

The objectives of this study were to evaluate prescription patterns to assess prescription preferences

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Funded by the Immunology Research Fund of the Department of Pediatrics, National University Health System, Singapore

The authors have no conflicts of interest to declare pertaining to this article

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and adherence to established international guidelines in a tertiary pediatric center.

METHODS

This is a retrospective study using data obtained from outpatient prescription databases of the University Children's Medical Institute, one of the two major tertiary centers for pediatric care in Singapore. An average of 33,444 children were seen per year from 2001 to 2010 at this facility for various medical reasons. Only patients aged 0–18 years, during the years 2001–2010, were included. Prescription data of drugs in the nebulized and inhaler form (nebulizers, metered-dose inhalers, Turbuhalers and Accuhalers) under the categories of short-acting β -agonists (SABAs), ICS, combination therapy (LABA–ICS), and tablets of montelukast (leukotriene receptor antagonist), was obtained. Prescription data belonging to one unique identifier (patient) were collapsed into one entry for each class of drug in each year to eliminate duplicate entries. Children with missing demographic data were included in the overall analysis but were excluded when analyzing in demographic-specific subgroups (up to 0.3% of the entire database).

Prescription of inhaled SABA was taken to be a surrogate of current wheeze. The prescription of both an SABA and one controller (any type of ICS, including LABA–ICS combinations) medication was taken as a surrogate of asthma requiring regular controller therapy. When reviewing patients on montelukast, only those who were also on SABA concomitantly were considered, because montelukast is also prescribed for conditions such as allergic rhinitis. The number of patients in each year was adjusted for the total outpatient visits for any reason (including asthma), at the pediatric clinics of the same year at the hospital; these data were shown per 10,000 outpatient visits for any reason.

Additionally, the total number of drug canisters/tablets/nebulized forms was known for years 2005–2010. To calculate the canister equivalents of nebulized medications, the following assumptions were made. For SABA, one canister (200 actuations) with an average dose of 2 actuations was assumed to contain 100 doses. Nebulized medication for SABA came in two forms: single-dose (2.5 mg) vials and 10-mL bottles of 0.5% respirator solution. Therefore, 100 single-dose vials were assumed as equal to one canister equivalent. A salbutamol 10-mL bottle at the standard dose of 0.5 mL (0.25 mg) in a child was assumed to contain 20 doses; thus, 5 bottles were considered to be equivalent to 100 doses or one canister equivalent. For ICS, the nebulized medication comprises single-use vials of budesonide. The most common ICS inhalers prescribed at our center were beclomethasone and budesonide (each with 50

μg /actuation and 200 actuations/canister) and were assumed to have 100 doses (100 μg /dose). Hence, 100 single-dose vials were taken to be one canister equivalent. Ratios of the number of canister equivalents (*i.e.*, total canisters plus nebulizing solutions) of ICS, canisters of LABA + ICS, and montelukast prescriptions, to canister equivalents of SABA in each year were calculated to determine the trends in prescription and proportion of controller medications among children with current wheeze.

The number of patients and age subgroups receiving nebulized SABA and ICS was evaluated as a proportion of the total patient numbers receiving SABA and ICS, respectively, in their respective years. Among the group receiving nebulized ICS, for purposes of determining number of patients on controller treatment, patients whose total canister equivalent prescription of ICS in any year were equal to one or more, were considered to be on controller treatment in that year. Those, whose total canister equivalent prescription of ICS fell below one for that year, were not considered to be on controller treatment in that year.

Approval, plus a waiver of consent, was obtained from the National Healthcare Group Research and Development Office, Domain-Specific Review Board.

Statistical Analysis

Linear regression was used to determine temporal trends in prescription of asthma drugs. Subgroup analysis by demographic factors, such as age group in a given year, race, and gender, was also performed. The children were divided into three age categories, *viz.*, infants (<1 year old), preschoolers (1–5 years old), and school-going children (>5 years old). Race categories included the three main local ethnic groups: Chinese, Malay, Indian, and others (ethnicity other than the previous three stated).

RESULTS

The demographics of the study cohort are shown in Table 1. Male subjects were predominant over female subjects (61.1% versus 38.6%); the preschooler group (age, 1–5 years) was larger (49.5%) than the school-going group (38.7%). The ethnic groups were reflective of the local population, with Chinese (54.9%) being the most common, followed by Malays (19.5%), Indians (12.2%), and then the other minor ethnic groups.

Table 2 shows the results of the statistical analysis for each drug group by patient number and drug/SABA ratio, for the whole cohort and age subgroups.

Short-Acting β -Agonists

There was an increasing trend. By the year 2010, prescriptions of SABA had increased significantly by 72% (from 344 to 592 patients per 10,000 outpatient

Table 1 Demographics of population studied
(*n* = 10,250)

Gender	
Male	6266 (61.1%)
Female	3955 (38.6%)
Missing values	29 (0.3%)
Age category	
Infants (<1 yr old)	1217 (11.9%)
1–5 yr	5069 (49.5%)
>5 yr	3964 (38.7%)
Race	
Chinese	5624 (54.9%)
Malays	2000 (19.5%)
Indians	1247 (12.2%)
Others	1358 (13.2%)
Missing values	21 (0.2%)

visits) for the whole cohort ($p = 0.016$), compared with the year 2001. The increase was also significant in male subjects (+77.5%; $p = 0.007$), preschoolers (age, 1–5 years; +77.2%; $p = 0.027$), school-going children (>5 years; +58.9%; $p = 0.008$), Indians (+84.8%; $p < 0.001$), and minorities (+349%; $p < 0.001$).

Nebulized SABAs

For the whole cohort, SABA in nebulized form took up a significant proportion of all patients receiving SABA; as many as 35.7% of the patients who were prescribed SABA received nebulized forms. After 2005, this trend declined gradually to as low as 3.1% of the whole cohort. Among the age groups, nebulized SABA made up the largest proportion by far in infants, peaking at 79.8% of the infant subgroup in 2006. This proportion declined thereafter to 8.8% by 2010. The declining trend in both the whole cohort and the infant subgroup was not statistically significant (trend for entire cohort, 2006–2010: $p = 0.157$; infant subgroup, 2006–2010: $p = 0.17$).

Inhaled Corticosteroids

The total patient numbers prescribed ICS increased from 2001 to 2003, but thereafter remained static. Consequently, the overall increase (+41.1%, from 251 patients per 10,000 outpatient visits in the year 2001, to 353 patients per 10,000 outpatient visits in the year 2010) was not statistically significant. In the subgroup analysis, significant increases between 2001 and 2010 were seen in the school-going children (>5 years; +60.0%; $p = 0.019$); in Malays (+73.6%; $p = 0.035$), in Indians (+74.5%; $p = 0.006$), and in the minorities (+302.2%; $p < 0.001$).

ICS/SABA Ratios

The ratio of prescribed ICS canisters to the number of SABA canisters prescribed increased from 2005 to 2010,

but this was not significant. In the subgroups, the increase was significant only in children of school-going age (>5 years; +72.4%; $p = 0.042$). Among the ethnic groups, there were significant increases only in Indians (+49.7%; $p = 0.017$). The ratios range between 0.74 and 1.25 for the whole cohort, and 0.69 and 1.19 for the school-going age (>5 years) group.

Nebulized ICSs

Nebulized ICS was prescribed much less frequently than nebulized SABA. The peak of 10.2% of the whole cohort of patients receiving ICS occurred in 2004, declining thereafter to 1.6% of the whole cohort in 2010. Among the age groups, nebulized ICS made up the largest proportion by far in infants, peaking at 70.3% of the infant subgroup in 2005, and declining to 16.1% by 2010. The declining trend in both the whole cohort and the infant subgroup was not statistically significant (trend for entire cohort 2005–2010: $p = 0.051$; infant subgroup 2005–2010: $p = 0.068$).

LABA-ICS Combinations

There was an increasing trend from 2001 to 2005, but this was statistically not significant. From 2006 to 2010, the overall trend decreased. The patient numbers decreased (from 83 per 10,000 outpatient visits in 2001, to 56 per 10,000 outpatient visits in 2010) by 32.4% ($p = 0.003$). The decrease was also significant in the following subgroups: in male subjects, by 33.0% ($p = 0.002$); in female subjects, by 31.4% ($p = 0.003$); preschoolers (age 1–5 years), by 66.5% ($p = 0.043$; Fig. 1); Chinese, by 47.5% ($p = 0.004$); Malays, by 28.3% ($p = 0.009$); and in the minor races by 29.5% ($p = 0.039$).

LABA-ICS Combinations/SABA Ratios

The trend in the ratio of number of canisters of LABA-ICS to that of SABA was static ($p > 0.05$). The only significant decrease was seen in the preschoolers (aged 1–5 years; –54.4%; $p = 0.049$; Fig. 1).

Montelukast

From 2001 to 2005, no significant trends upward or downward were noted. However, over 2006–2010, there was a significant rise (from 37 patients per 10,000 outpatient visits in 2006, to 109 patients per 10,000 outpatient visits in 2010) by 194.6% ($p = 0.009$) in montelukast use as adjunct therapy in the patients who were also prescribed SABA. This increase was significant in both genders: 175.5% in male subjects ($p = 0.003$) and 227.5% in female subjects ($p = 0.021$). Preschoolers (aged 1–5 years) and school-age children (>5 years) had a significant rise between 2006 and 2010 (+222.4%, $p = 0.007$, and +262.5%, $p = 0.043$, respectively; Fig. 2). There was an increase in prescriptions of montelukast to patients of Chinese (+171.7%; $p =$

Table 2 Changes in prescriptions and ratios between 2001 and 2010

Drug Type Analysis (Period)	Change across Period (%)	β -Coefficient of Regression Line	<i>p</i> Value
Changes in SABA and ICS prescriptions and ratios between 2001 and 2010			
SABA			
Patient numbers (2001–2010)*#	+72.0%	+26.8	0.016
Patient numbers, aged <1 yr (2001–2010)	+201.0%	+3.39	0.083
Patient numbers, aged 1–5 yr (2001–2010)*	+77.2%	+9.67	0.027
Patient numbers, aged >5 yr (2001–2010)*	+58.9%	+13.8	0.008
ICS			
Patient numbers (2001–2010)	+41.1%	+7.00	0.172
Patient numbers, aged <1 yr (2001–2010)	–43.4%	–0.655	0.054
Patient numbers, aged 1–5 yr (2001–2010)	+31.6%	+1.37	0.576
Patient numbers, aged >5 yr (2001–2010)*	+60.7%	+6.16	0.027
ICS/SABA ratio (2005–2010)	+52.5%	+0.0560	0.09
ICS/SABA ratio, aged <1 yr (2005–2010)	+168.1%	+0.138	0.177
ICS/SABA ratio, age 1–5 yr (2005–2010)	+37.2%	+0.0734	0.192
ICS/SABA ratio, age >5 yr (2005–2010)*	+72.4%	+0.0984	0.042
Changes in LABA–ICS and montelukast prescriptions and ratios between 2001 and 2010			
LABA–ICS			
Patient numbers (2001–2005)	+272.3%	+16.8	0.236
Patient numbers (2006–2010)*	–32.4%	–7.24	0.003
Patient numbers, age <1 yr (2006–2010)	0	0	NA
Patient numbers, aged 1–5 yr (2006–2010)*	–66.5%	–4.27	0.043
Patient numbers, aged >5 yr (2006–2010)	–15.6%	–3.00	0.183
LABA–ICS/SABA ratio (2005–2010)	+8.2%	+0.00650	0.626
LABA–ICS/SABA ratio, aged <1 yr (2005–2010)	0	0	NA
LABA–ICS/SABA ratio, aged 1–5 yr (2005–2010)*	–54.4%	–0.0169	0.049
LABA–ICS/SABA ratio, aged >5 yr (2005–2010)	+42.0%	+0.0238	0.285
Montelukast			
Patient numbers (2001–2005)	–45.1%	–7.53	0.142
Patient numbers (2006–2010)*	+194.6%	+17.9	0.009
Patient numbers, age <1 yr (2006–2010)	+29.7%	+0.712	0.137
Patient numbers, aged 1–5 yr (2006–2010)*	+222.4%	+12.5	0.007
Patient numbers, aged >5 yr (2006–2010)*	+262.5%	+4.76	0.043
Montelukast/SABA ratio (2005–2010)*	+345.3%	+1.08	0.032
Montelukast/SABA ratio, aged <1 yr (2005–2010)	+134.5%	+1.10	0.172
Montelukast/SABA ratio, aged 1–5 yr (2005–2010)*	+332.4%	+1.90	0.029
Montelukast/SABA ratio, aged >5 yr (2005–2010)	+565.7%	+0.462	0.089

*Indicates statistically significant temporal trend.

ICS = inhaled corticosteroid; LABA = long-acting β -agonist; SABA = short-acting β -agonist.

0.014), Indian (+357.7%; $p = 0.01$), and minority (+181.6%; $p = 0.001$) ethnicities, but not in the Malays.

When the entire period from 2001 to 2010 was evaluated, one additional trend stood out: the increase in prescriptions to infants, from 0 patients in the year 2001, to 8.92 patients per 10,000 outpatient visits ($p < 0.001$) in the year 2010.

Montelukast/SABA Ratios

There was an increase in the ratio of number of tablets of montelukast to the number of canisters of

SABA by 345.3% ($p = 0.032$) from the year 2005 to 2010. Similarly, this ratio increased by 368.5% in male patients ($p = 0.003$), 332.4% in preschoolers (aged 1–5 years; $p = 0.029$; Fig. 2), and 330.8% in Chinese patients ($p = 0.029$).

DISCUSSION

We observed a rising trend of patient numbers receiving SABA over the study period from 2001 to 2010. This could reflect an increasing prevalence of childhood wheezing at our hospital over this time period

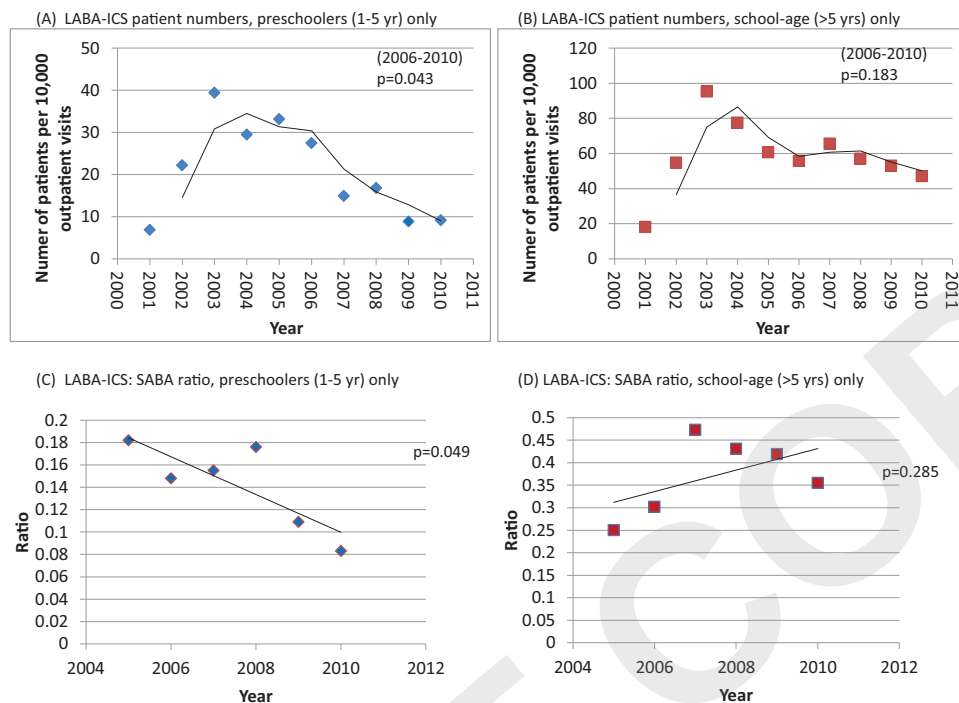


Figure 1. Long-acting β -agonist in combination with inhaled corticosteroid (LABA-ICS) patient trend, per 10,000 outpatient visits, and LABA-ICS/short-acting β -agonist (SABA) ratio. Linear regression was used to determine the significance of temporal trends. (A) Number of patients per 10,000 outpatient visits for any reason to the hospital, who were prescribed LABA-ICS, is shown for the years 2001–2010, in the preschool age subgroup. (B) Number of patients per 10,000 outpatient visits for any reason to the hospital, who were prescribed LABA-ICS, is shown for the years 2001–2010, in the school-age subgroup. (C) Ratio of LABA-ICS canisters to SABA canisters, prescribed from 2005 to 2010, in the preschool age subgroup. (D) Ratio of LABA-ICS canisters to SABA canisters, prescribed from 2005 to 2010, in the school-age subgroup.

but may also be caused by a change in prescription habits to use SABA for the treatment of childhood wheeze at this center. To our knowledge, there has not been other evidence that would point to one possibility over the other.

There was also an increasing trend in number of patients receiving any ICS per 10,000 outpatient visits, although this plateaued after 2003 and was not statistically significant for the cohort as a whole. There was a significant increase in patient numbers as well as ICS/SABA ratio in the school-going age group, who are more likely to have asthma; suggesting better adherence to guidelines recommending ICS as first line for asthma control.

However, the ICS/SABA ratios in the school-going age group appear to be low. The increase in SABA units prescribed each year in this age group matched or fell below those of ICS; with mean ratios below or $\sim$ 1:1 throughout this period (range, 0.69–1.19). Chong *et al.*¹² had shown that the controller/reliever ratios in primary care clinics for asthma could increase from 0.68, before the introduction of educational interventions with feedback to physicians, to 1.80 after such intervention. Others have also highlighted concerns regarding suboptimal prescription of ICS in children

with asthma.¹³ From a clinical perspective, ICSs may be underprescribed, for any number of reasons: patients may not be compliant, or the recognition for the need of controller therapy is lacking, or both. Even then, “optimal” controller/reliever ratios may not equate to good asthma control. Rank *et al.*¹⁴ showed an improvement in asthma controller/total medication ratio and did not result in a difference in asthma exacerbation rates.

Nebulized medication, especially SABA, is commonly used in the treatment of acute asthma exacerbations worldwide. After 2005, despite the increasing numbers of patients being prescribed SABA and ICS, there was a move away from the use of nebulized medication. The British Guideline on the Management of Asthma¹⁵ specifically states that a “pMDI and spacer is at least as good as a nebulizer in treating mild and moderate asthma exacerbations in children and adults,” in keeping with current evidence.^{16–19} The main advantages of an inhaler and spacer device over nebulizers include the convenience, decreased time required for setup and use, and absence of need for a power source.

There was an increasing trend toward prescribing montelukast after 2005, with an accompanying in-

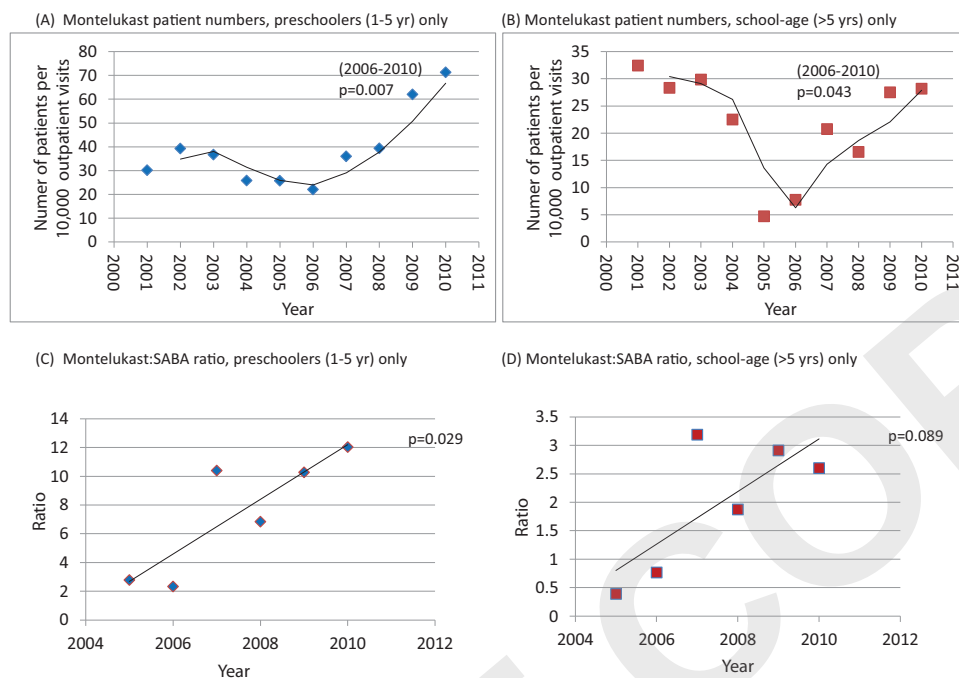


Figure 2. Montelukast patient trend per 10,000 outpatient visits, and montelukast/ short-acting β -agonist (SABA) ratio. Linear regression was used to determine the significance of temporal trends. (A) Number of patients per 10,000 outpatient visits for any reason to the hospital, who were prescribed montelukast, is shown for the years 2001–2010, in the preschool-age subgroup. (B) Number of patients per 10,000 outpatient visits for any reason to the hospital, who were prescribed montelukast, is shown for the years 2001–2010, in the school-age subgroup. (C) Ratio of montelukast drug units (tablets) to SABA canisters, prescribed from 2005 to 2010, in the preschool-age subgroup. (D) Ratio of montelukast drug units (tablets) to SABA canisters, prescribed from 2005 to 2010, in the school-age subgroup.

crease in the montelukast/SABA drug unit ratio from 2006 to 2010. At the same time, there is a corresponding dip in patient numbers prescribed LABA–ICS combinations. This decrease was most prominent in the preschool age group. The recent tendency to move away from prescribing LABA in combination therapy, with a preference for using montelukast instead, could be caused by several reasons. The black box warning against LABA use was issued by the Food and Drug Administration in October 2005, and the few years thereafter through to 2009, have seen the publication of guidelines that did not recommend the use of LABAs, especially in young children. Montelukast has been shown to have a good safety profile, although there have been reports linking it to neuropsychiatric disorders.^{20–23} Studies have shown the efficacy and safety profile of the montelukast, with the need to customize step-up therapy in some children.^{24,25} The preference for montelukast among caregivers also lies in its ease of administration. Increases in montelukast therapy in 2005–2008, compared with 1999–2002, have been documented in the United States, although there was also a concomitant increase in LABA use in that same study.²⁶

One point of concern was the rise in infants being prescribed montelukast and SABA. This may reflect the lack of pharmacologic options in the management

of infant wheeze. Both ICS and montelukast are approved for use above the age of 1 year. Montelukast is, however, labeled for use above the age of 6 months for allergic rhinitis.

Another significant trend was the increased use of montelukast in school-age children receiving SABA. One worrisome possibility could be an increasing preference for the use of montelukast over ICS for asthma. However, montelukast is also used to treat concomitant allergic rhinitis and ~75–90% of patients with asthma also have concomitant allergic rhinitis.^{27–30} Wang *et al.*³¹ showed an increasing trend in the coexistence of asthma and allergic rhinitis in children in Singapore, with a predilection for the male gender as compared to females and in Chinese compared with the other major ethnic groups. This may explain in part the significantly increased montelukast/SABA ratios in these two subgroups.

The Indian subgroup was the only ethnic group that did not show a decreasing trend in LABA–ICS prescriptions, and also had a big jump in patient numbers receiving montelukast. These observations may be explained by the more severe asthma in this ethnic group.^{32–34} The Malay subgroup was the only subgroup that did not show significant changes in montelukast patient numbers; this may be related to the higher expense of montelukast. It has been previously

shown that the Malay ethnic group makes less use of health services.³³

Several studies have shown poor concordance of actual prescription patterns with location-specific guidelines or international guidelines.^{35–40} A recent review⁴¹ that looked at both the impact of guidelines as well as the interventions on clinical practice shows mixed results. Although our study did not address the impact of asthma prescription drugs to asthma outcomes, our results show prescription trends that suggest successful implementation of established guidelines in a tertiary setting and reflect the impact of clinical practice guidelines that are focused in young children on prescription patterns in our institution. ICS was still by far the most commonly prescribed controller. At the same time, there is a significant decrease in the prescription of combination therapy (LABA–ICS) in children aged 1–5 years old with current wheeze from 2005 to 2010. This trend is unlikely to change in the near future because the latest Cochrane review still pointed toward an additional three children per 1000 who suffer a nonfatal serious adverse events on combination therapy in comparison with ICS over 3 months.¹¹

In conclusion, this study provides insight into prescription trends of asthma medications in childhood in a tertiary institute in Singapore. The change in trends appears to be influenced by changes in guidelines, reflecting evidence-based clinical practices.

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