THE USE OF LONG-ACTING β_2-AGONISTS AS MONOTHERAPY IN CHILDREN AND ADULTS

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ABSTRACT

Background
In asthma, it is recommended that long-acting β2-agonists (LABAs) not be used as monotherapy, but, be used with inhaled corticosteroids (ICS) to minimize the risk of serious adverse events.

Objective
To test the hypothesis that if clinical recommendations were followed, LABA monotherapy would not occur in children and would only occur in COPD, where it is not contraindicated.

Methods
We analyzed LABA and ICS dispensing for British Columbians with respiratory conditions in 2004. LABA use was classified as "LABA Monotherapy", "LABA with Concurrent ICS", or "Mixed" (LABA use, occasional ICS use). Using physician and hospital billing records, children < 18 years were classified as having "asthma" or "other respiratory condition". Adults were classified as having "asthma", "COPD", "asthma and COPD", or "other respiratory condition". We calculated the prevalence of LABA monotherapy, and the association between LABA monotherapy and diagnosis, age, gender, and location of residence.

Results
LABA monotherapy occurred in 3.4% (n=140) of pediatric and 3.9% (n=1837) of adult LABA users and in 3.4% of children with asthma and 3.0% of adults with asthma. In children, LABA monotherapy was associated with female gender (odds ratio (OR) 1.62; 95% confidence interval (CI) 1.14, 2.82; p<0.0065) and adolescence (age 12-18 years; 2.30; CI 1.53,3.46; p<0.0001). In adults, LABA monotherapy was associated with a COPD diagnosis, and being greater than 60 years old (p<0.0001).

Conclusion
LABA monotherapy occurs in children and adults. LABA monotherapy in children, especially in girls and adolescents, could expose them to serious adverse events and requires further study.

Key Words: *Adrenergic beta-2 receptor agonists; asthma; drug utilization; pediatrics; pulmonary disease, chronic obstructive*

Long-acting β_2-agonists (LABAs) are inhaled medications designed to relax airway smooth muscle by stimulating airway β_2-receptors. They were first introduced in Canada in 1994 for use in asthma. The purpose of LABAs is to reduce respiratory symptoms in patients whose symptoms

are not well-controlled on inhaled corticosteroids. Past and recent guidelines in Canada[1-3] and internationally[4] have clearly stated that LABAs are not to be used as monotherapy in patients with asthma, but should always be used in conjunction with an inhaled corticosteroid (ICS) or other controller device.

The recommendation against LABA monotherapy for asthma patients is due in part to safety concerns that arose shortly after their introduction. There have been several prospective randomized clinical trials (RCTs), retrospective analyses of manufacturers' trial data, and meta-analyses designed to assess the safety of LABAs. The SMART study in the U.S.[5] was a large (n=26,355) RCT designed to assess the safety of salmeterol in patients with asthma. The investigators reported a small but significant increase in respiratory-related deaths and 'life-threatening experiences' with LABA use, and reported an increased risk in African-Americans. A subsequent meta-analysis of 19 RCTs confirmed these findings.[6] In 2003, Health Canada and the U.S. Food and Drug Administration (FDA) responded with advisories and "Dear Health Care Professional" letters which summarized the potential risks of LABA use and reiterated that LABAs should not be used as monotherapy. These advisories were reissued in 2010. However, although recommendations against LABA monotherapy have been clearly and repeatedly stated, it is well reported that clinical practice guidelines for asthma are often not followed.[7-9]

Another factor which influences LABA monotherapy use is that the indication for LABA has since expanded to include chronic obstructive pulmonary disease (COPD), and LABA monotherapy in COPD is *not* contraindicated.[10,11] Asthma can often be confused with or co-exist with COPD[11] which may increase the likelihood of LABA monotherapy occurring in patients with asthma. In this study, we sought to measure the extent of LABA monotherapy in children and adults with respiratory disease in British Columbia, Canada. We hypothesized that if clinical practice guidelines and warnings were followed, 1) LABA monotherapy would be associated with a COPD diagnosis and not an asthma diagnosis and as such, 2) LABA monotherapy would not occur in the pediatric respiratory population.

METHODS

We analysed LABA data from 2004, acquired from provincial administrative health service utilization databases. Pharmaceutical dispensing data from 2004 is the most current data available to B.C. researchers, and Canadian asthma guidelines advising against LABA monotherapy were issued in 2001[1] and again in early 2004.[12] The BC Ministry of Health Services maintains administrative health service utilization databases as part of their comprehensive medical insurance for provincial residents.[13-15] Each resident receives a unique Personal Health Number (PHN) upon registering for provincial medical insurance. For research purposes, the PHN is replaced by an anonymized individual identifier which enables linkage of the different health databases. Individuals without unique PHNs who are not included in the administrative databases include inmates, members of the armed forces, and First Nations, Metis and Inuit peoples living on reserve (in Canada, this is estimated to be approximately 1-2% of the population[16]). This study was approved by the University of British Columbia Research Ethics Board and internal review boards.

We analyzed administrative data for all BC residents, age 5 years and older, who had seen a physician[14] or had been hospitalized[15] for any one of 8 respiratory diagnoses, which included asthma, COPD, bronchiectasis, and bronchitis (Table 1a), from the years 1995 to 2004. For each patient, we acquired demographic data; area of residence; prescription respiratory medication (drug, dose and date of dispensing); and details of any physician visit or hospitalization for respiratory-related events (including pneumonia, upper respiratory tract infections and influenza). Prescription data was acquired from the PharmaNet Database[13], which records prescription information for ALL medications dispensed to BC's residents, regardless of payer. To be included in this study, patients had to be residents of BC for at least 271 days (or 75% of the year) in 2004.

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TABLE 1a ICD9 Respiratory Codes to Identify the Initial Cohort [13-15]

	ICD9 Code	Description
1	466	Acute bronchitis
2	472	Chronic pharyngitis
3	490	Bronchitis, not specified as acute or chronic
4	491	Chronic bronchitis
5	492	Emphysema
6	493	Asthma
7	494	Bronchiectasis
8	496	Chronic airways obstruction, not elsewhere classified

TABLE 1b ICD9 Codes to Identify Respiratory-related Physician Visits or Hospitalizations in our Initial Cohort of Respiratory Patients[13-15]

	ICD9 Code	Description	Assigned Diagnostic Group
1	460	Acute nasopharyngitis	Acute Upper Respiratory Disease
2	465	Acute upper respiratory tract infection	Acute Upper Respiratory Disease
3	466	Acute bronchitis	Acute Lower Respiratory Disease
4	472	Chronic pharyngitis	Chronic Upper Respiratory Disease
5	477	Allergic rhinitis	Chronic Upper Respiratory Disease
6	480	Viral pneumonia	Acute Lower Respiratory Disease
7	481	Pneumococcal pneumonia	Acute Lower Respiratory Disease
8	482	Other bacterial pneumonia	Acute Lower Respiratory Disease
9	485	Bronchopneumonia	Acute Lower Respiratory Disease
10	487	Influenza	Acute Lower Respiratory Disease
11	490	Bronchitis, not specified as acute or chronic	Chronic Lower Respiratory Disease
12	491	Chronic bronchitis	COPD
13	492	Emphysema	COPD
14	493	Asthma	Asthma
15	494	Bronchiectasis	Chronic Lower Respiratory Disease
16	496	Chronic airways obstruction, not elsewhere classified	COPD

ICD9 = International Classification of Diseases, 9th edition; ICD10 = International Classification of Diseases, 10th edition; COPD = chronic obstructive pulmonary disease

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We then identified LABA users in this cohort. To be considered a LABA user, a patient must have received at least 1 dispensed prescription for a LABA medication in the year 2004. Approved LABA medications in BC were:

1. salmeterol;
2. formoterol;
3. salmeterol/flucticasone combination product; and
4. formoterol/budesonide combination product.

Approved ICS medications in BC are:

1. fluticasone;
2. budesonide;
3. salmeterol/fluticasone;
4. formoterol/budesonide; or
5. beclomethasone.

We divided the LABA users into one of three groups depending on their LABA monotherapy status:

Group 1: LABA monotherapy

These patients received at least 1 LABA dispensed prescription with no ICS dispensed prescription in 2004 or in the last 3 months of 2003. To be classified as having received LABA monotherapy, a patient must have received at least 1 dispensing for a LABA in 2004, with no dispensing of an ICS in 2004 or during the last 3 months of 2003.

Group 2: LABA and ICS concurrent therapy

LABA monotherapy never occurred. These patients either were always dispensed LABA/ICS combination products (both medications delivered in the same canister), or received every LABA dispensing with an ICS dispensing on the same day.

Group 3: LABA and ICS – mixed

These patients received both ICS and LABAs at some point during 2004, but these medications were not always dispensed at the same time. Therefore, these patients had some periods of LABA monotherapy and some periods when LABAs and ICSs were used concurrently.

For all LABA users, we identified the geographical area of residence. As we had access to LABA use for the population of chronic lung disease patients for the entire province, identifying the geographical area allowed us to determine if LABA monotherapy was associated with a particular region of the province or occurred province-wide. Each patient was categorized as a resident of 5 distinct areas of the province: 1) Northern BC; 2) Interior of BC; 3) Vancouver Island; 4) Vancouver suburbs; and 5) City of Vancouver.

All LABA users were assigned a diagnostic category. To classify each patient into one diagnostic category for 2004, we analyzed the respiratory-related physician visit and hospitalization records for each LABA user, from 1995 to 2004. Each physician record and hospitalization record had one or more of 16 possible respiratory ICD9 codes listed in Table 1b. We assigned a Diagnostic Group for each of these ICD9 codes. A given patient could have many diagnoses over the time period, but for the purposes of assigning a diagnosis that was relevant to LABA therapy, we followed the algorithm in Figure 1 We categorized a patient as having COPD if they were 35 years or older and had one physician visit or hospitalization using ICD9 codes 491.xx (chronic bronchitis), 492.xx (emphysema), or 496.xx (chronic airways obstruction, not elsewhere classified) in that time period. We categorized patients as having asthma if they had one physician visit or hospitalization with the ICD9 code 493. Patients with both codes were categorized as asthma/COPD. Patients with neither a COPD or asthma code were categorized based on the algorithm in Figure 1. As COPD is rare in individuals under 35 and should not be diagnosed in the paediatric population, if a patient <35 years old received a COPD code and an asthma code, they were categorized as asthma. If they received a COPD code only, they were categorized as 'Chronic Lower Respiratory Disease'.

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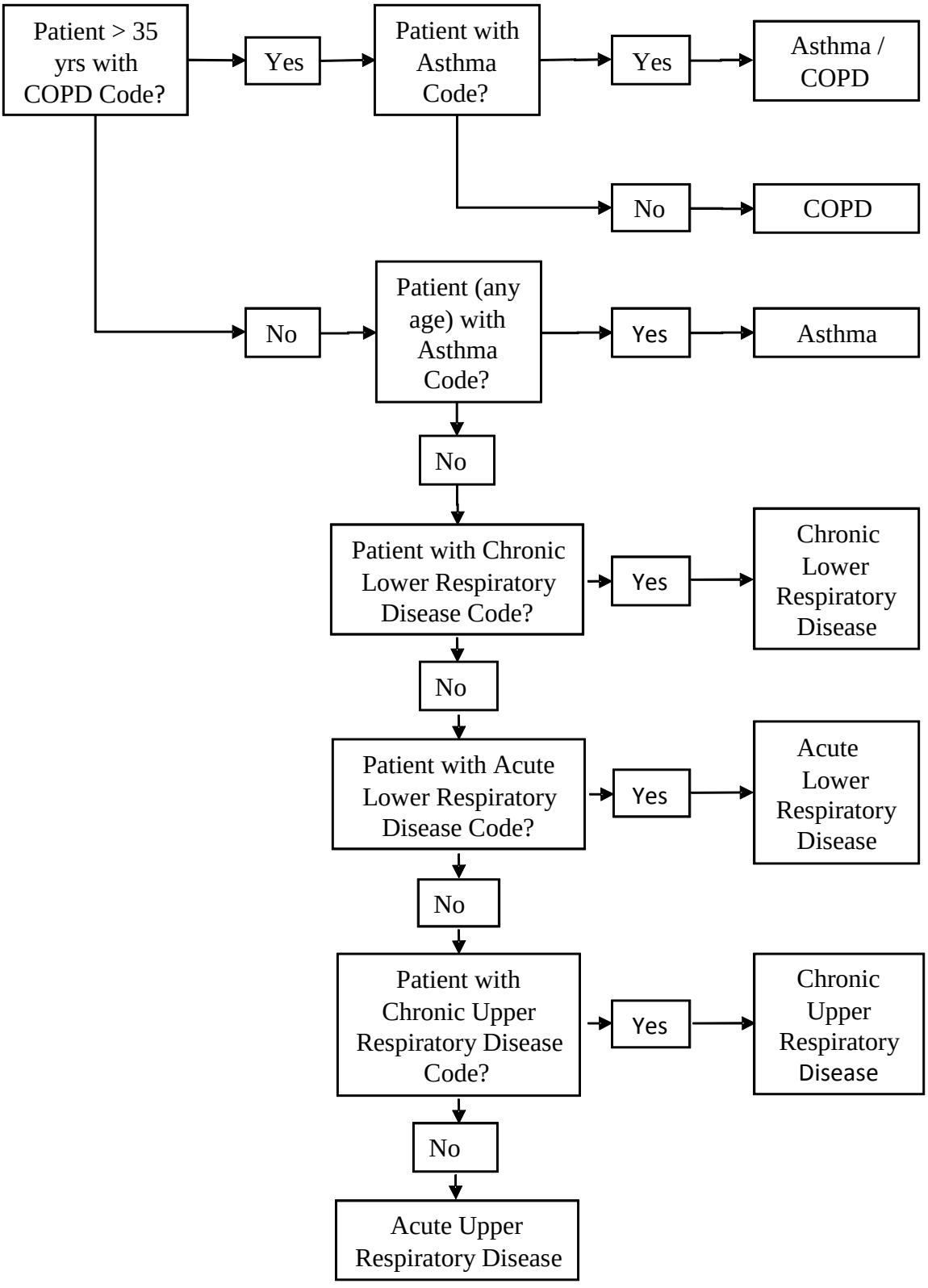

FIG. 1 Algorithm for Categorizing Respiratory Diagnosis

Data Analysis

We measured the prevalence of LABA monotherapy among LABA users in British Columbia in 2004. The characteristics of LABA users are described using means and percentages as appropriate. We analyzed the data from children (5-18 years) and from adults (19 years and older) separately. We calculated the prevalence of LABA monotherapy in BC overall and within each health region in the province. For paediatric patients, we used multiple logistic regression models to measure the association between LABA monotherapy (yes/no) and diagnosis, age, gender and health authority. Similarly, for the adult population, we used multiple logistic regression to test the hypothesis that LABA monotherapy (yes/no) was significantly associated with a diagnosis of COPD, adjusting for age, gender and health authority and calculated adjusted odds ratios and 95% confidence intervals. A p-value of less than 0.05 was considered significant. Model fit was assessed with the Hosmer-Lemenshow test.[17]

RESULTS

There were 50,828 British Columbians with a respiratory diagnosis who received at least 1 prescription for a LABA in 2004. The majority (74%) of LABA users were adults over the age of 40 years. The gender distribution by age for individuals who were dispensed a LABA is depicted in Figure 2. For children, the majority (63%) of LABA users in the youngest age group (5-11 years) were boys. This trend was reversed by adulthood; for each adult age category more women than men received at least one or more LABA dispensed prescription.

FIG. 2 Gender Distribution, by Age Group, of LABA Users, based on data acquired from the BC Ministry of Health[13-15]

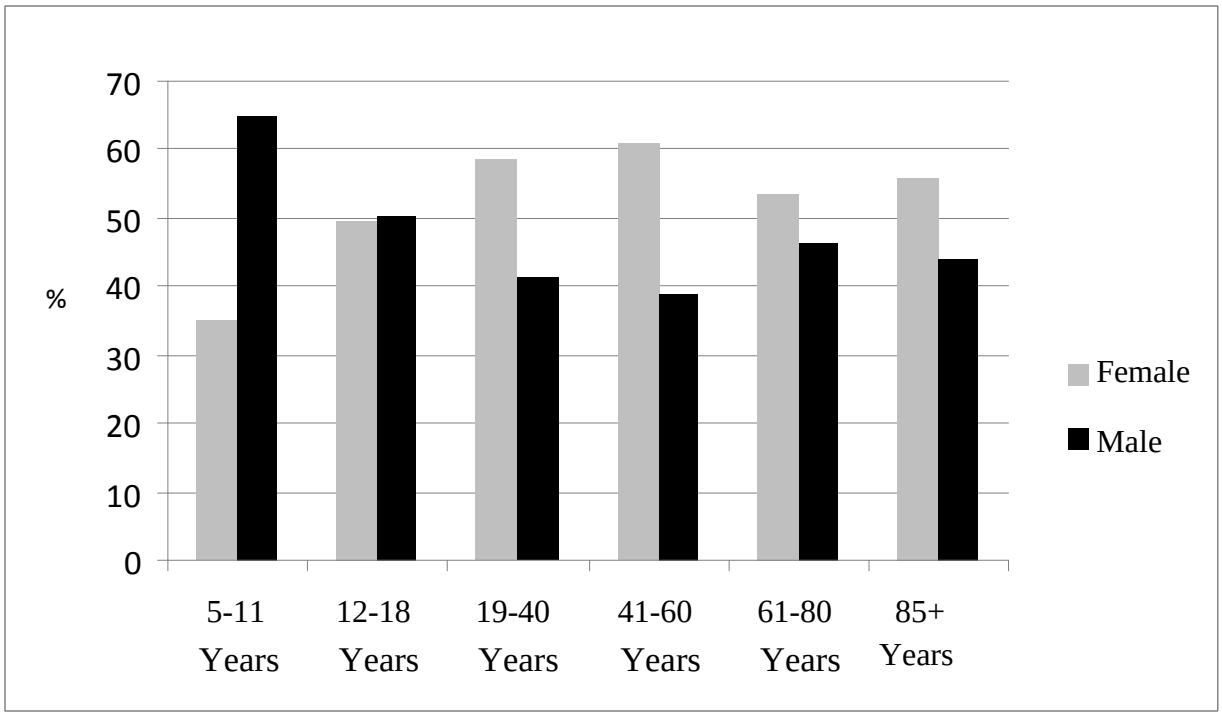

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TABLE 2 Gender and Age Characteristics of LABA Users, by Group, based on data acquired from the BC Ministry of Health[13-15]

	Group 1 LABA Monotherapy (never used ICS)	Group 2 LABA with concurrent ICS*	Group 3 Mixed (LABA and ICS use but not always concurrently)
n (% of sample)	1,977 (3.9%)	42,983 (84.6%)	5,868 (11.5%)
Female (% within Group)	56.1%	54.8%	58.1%
Age, Mean (SD)	59.8 (21.0)	52.8 (21.0)	63.2 (18.7)
Age Groups, n (% within Group)			
4-11	31 (1.6%)	1575 (3.7%)	95 (1.6%)
12-18	109 (5.5%)	2209 (5.1%)	134 (2.3%)
19-40	238 (12.0%)	8031 (18.7%)	471 (8.0%)
41-60	487 (24.6%)	14150 (32.9%)	1457 (24.8%)
61-80	827 (41.8%)	13538 (31.5%)	2766 (47.1%)
80+	285 (14.4%)	3480 (8.1%)	945 (16.1%)
Age Range	5-98	5 - 105	5-100
Diagnosis (% within Group)			
▪ Asthma	38.2 %	51.3 %	34.1 %
▪ COPD	20.0 %	7.5 %	9.5 %
▪ Asthma / COPD	32.3 %	32.8 %	54.5 %
▪ Chronic Lower Respiratory Disease	0.35 %	0.20 %	0.20 %
▪ Acute Lower Respiratory Disease	8.60 %	7.9 %	1.72 %
▪ Chronic Upper Respiratory Disease	0.30 %	0.22 %	0.03 %
▪ Acute Upper Respiratory Disease	0.20 %	0.10 %	0.03 %

LABA = long-acting beta-2 agonist; ICS = inhaled corticosteroid; COPD = chronic obstructive pulmonary disease; BC = British Columbia; SD = standard deviation

* LABA use either as a combination product, or both LABA and ICS dispensed the same day

TABLE 3 Unadjusted and Adjusted Odds Ratios for Factors Associated with LABA Monotherapy in the Pediatric Population (age 5-18)

	Unadjusted Odds Ratio	95% CI	p	Adjusted Odds Ratio	95% CI	p
Sex						
Male	1.00			1.00		
Female	1.81	1.29, 2.55	0.0006	1.62	1.14, 2.82	0.0065
Age Group						
5-11 yrs	1.00			1.00		
12-18 yrs	2.51	1.67, 3.75	<0.0001	2.30	1.53, 3.46	<0.0001
Diagnosis of Asthma						
Yes	1.00			1.00		
No	1.01	0.53, 1.94	0.976	1.04	0.54, 2.00	0.915
Region of Province						
▪ North BC	1.00			1.00		
▪ Interior	0.89	0.43, 1.78	0.726	0.87	0.43, 1.78	0.704
▪ Vancouver Island	0.91	0.45, 1.81	0.771	0.91	0.45, 1.84	0.791
▪ Vancouver Suburbs	0.75	0.38, 1.47	0.402	0.80	0.41, 1.58	0.524
▪ Vancouver	0.62	0.30, 1.30	0.207	0.69	0.33, 1.46	0.330

LABA = long-acting beta-2 agonist; BC = British Columbia; CI = Confidence interval

The characteristics of the three LABA usage groups are shown in Table 2. LABA monotherapy in 2004 occurred in almost 2,000 individuals, or 3.9% of the population of LABA users. The majority of LABA users (79%) received a LABA as a combination product, i.e., received either formoterol/budesonide or salmeterol/fluticasone in a single inhaler. Individuals who used LABA monotherapy exclusively (Group 1) or intermittently (Group 3) were older than individuals who used LABAs and ICS medications together (Group 2). Over 90% of the patients in the three LABA user groups had a diagnosis of asthma, COPD, or asthma/COPD. For further analysis, the patients not in any of these three diagnostic categories was grouped in a "Respiratory-Other" category.

LABA Monotherapy

LABA Monotherapy in the Paediatric Age Group

3.4% of pediatric LABA users (n=140) received LABA monotherapy in 2004. An additional 229 children were in the LABA-mixed group, indicating they likely had some periods of time in 2004 when LABA monotherapy occurred. Most children (93%) who received a LABA had a diagnosis of asthma, regardless of group status. LABA monotherapy occurred in 3.4% (n=130) of paediatric asthma patients.

Odds ratios and 95% confidence intervals are shown in Table 3. LABA monotherapy was more likely to occur in girls compared to boys, and in the adolescent age group compared to children aged 5-11 years. Multiple logistic regression did not alter these findings; adolescents age 12-18 years were 2.3 times more likely to be on LABA monotherapy than the younger age group ($p<0.0001$). LABA monotherapy use was consistent throughout the province; there were no differences in LABA monotherapy associated with the 5 different health regions of BC (Northern BC, Central Interior of BC, Vancouver Island, Vancouver suburbs, and the City of Vancouver.)

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Two hundred twenty-nine children were in Mixed Group (LABA and ICS use occurred but not always concurrently). To better understand LABA and ICS use over the study period, we calculated the proportion of the year that each child received a dispensing of at least one LABA or ICS. A dispensing in each quarter of the year may indicate fairly consistent use of the medications over the whole year. Figure 3 shows the proportion of pediatric patients in the Mixed Group who received at least 1 dispensing of a LABA or ICS in each quarter of 2004. For each quarter, a higher proportion of children received at least one LABA dispensing versus an ICS dispensing. For each quarter, approximately 22-25% of children in the Mixed Group received a LABA without an ICS.

LABA Monotherapy in the Adult Age Group

3.9% of adult LABA users (n=1837) received LABA monotherapy in 2004. LABA monotherapy became more apparent in the older age groups - patients aged 80 years and older made up 14.4% of the LABA monotherapy group and 16.1% of the LABA-mixed group. In contrast, individuals 80 years and older comprised only 8.1% of subjects using LABA and concurrent ICS use (Table 2). LABA monotherapy occurred in 3.0% (n=685) of adults with asthma.

In the univariate analysis, LABA monotherapy was associated with male gender, older age, and a diagnosis of COPD (Table 4). In the multivariate analysis, male sex was no longer significantly associated with LABA monotherapy; however, LABA monotherapy continued to be associated with increasing age and a diagnosis of COPD. Similar to the paediatric population, there was no difference in LABA monotherapy use between the 5 different health regions of BC.

FIG. 3 Proportion of pediatric patients who received a LABA or ICS dispensing per quarter in 2004, based on data acquired from the BC Ministry of Health[13-15]

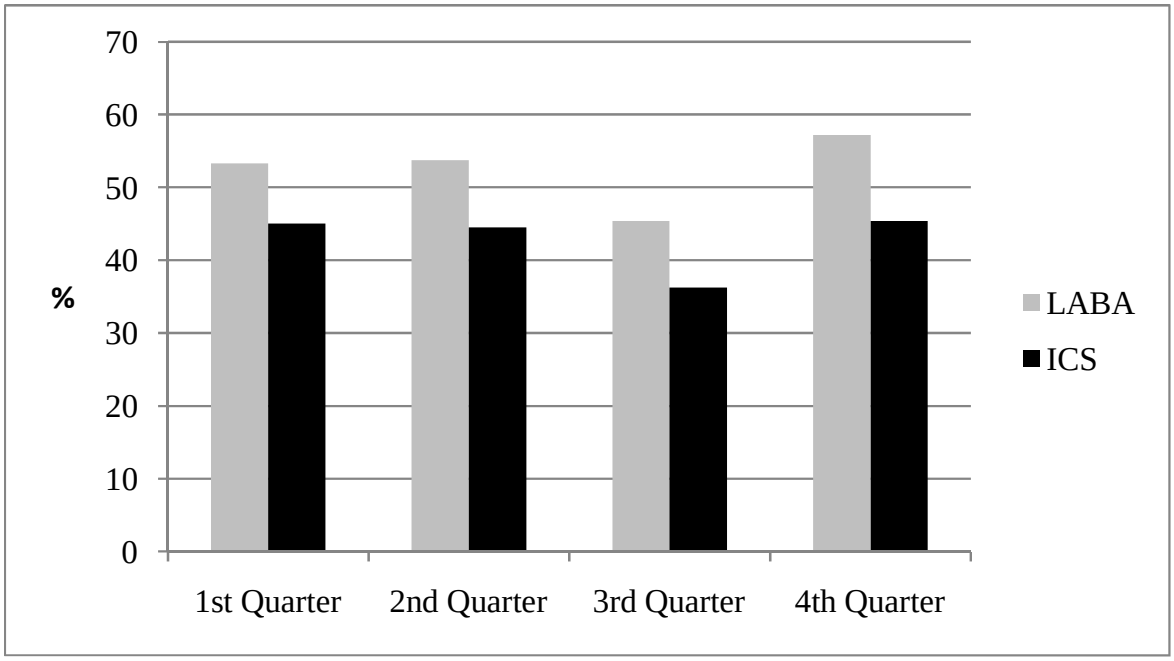

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TABLE 4 Unadjusted and Adjusted Odds Ratios for Factors Associated with LABA Monotherapy in the Adult Population (age 19+)

	Unadjusted Odds Ratio	95% CI	p	Adjusted Odds Ratio	95% CI	p
Sex						
Male	1.00			1.00		
Female	0.89	0.81, 0.97	0.011	0.961	0.87, 1.06	0.412
Age Group						
19-40 yrs	1.00			1.00		
41-60 yrs	1.12	0.95, 1.31	0.176	1.067	0.91, 1.25	0.424
61-80 yrs	1.81	1.57, 2.10	<0.0001	1.51	1.29, 1.78	<0.0001
80+ yrs	2.30	1.93, 2.74	<0.0001	1.83	1.51, 2.22	<0.0001
Diagnosis						
▪ COPD	1.00			1.00		
▪ Asthma	0.29	0.26, 0.33	<0.0001	0.39	0.33, 0.45	<0.0001
▪ Asthma/COPD	0.35	0.31, 0.40	<0.0001	0.37	0.33, 0.43	<0.0001
▪ Other Respiratory Condition	0.48	0.40, 0.58	<0.0001	0.59	0.49, 0.72	<0.0001
Region of Province						
▪ North BC	1.00			1.00		
▪ Interior	1.24	0.97, 1.58	0.082	1.07	0.84, 1.37	0.564
▪ Vancouver Island	1.05	0.83, 1.34	0.670	0.96	0.75, 1.22	0.721
▪ Vancouver suburbs	0.90	0.71, 1.14	0.365	0.86	0.68, 1.09	0.204
▪ Vancouver	0.98	0.77, 1.25	0.880	0.96	0.75, 1.22	0.563

LABA = long-acting beta-2 agonist; CI = confidence interval; COPD = chronic obstructive pulmonary disease; BC = British Columbia

DISCUSSION

This study was designed to investigate the extent of LABA monotherapy use in children and adults with respiratory disease living in British Columbia, Canada. We hypothesized that LABA monotherapy would only occur in adult patients. Our reasoning was that LABA monotherapy is not currently contraindicated in COPD, and COPD does not occur in paediatric populations. However, we found that LABA monotherapy use occurred in the paediatric population as well as the adult population. Although the actual numbers were not large (n=140 for consistent LABA monotherapy, and n=369 for consistent and intermittent LABA monotherapy use), if these proportions remained stable and were extrapolated to the Canadian population this would result in several thousand Canadian children exposed to LABA monotherapy each year, in direct contravention of published guidelines on safe LABA use. The strength of this study includes the use of the comprehensive PharmaNet database[13], which provides actual counts of LABA dispensed prescriptions, not estimates, for the entire province.

To our knowledge this is the first report of the occurrence of post-market LABA monotherapy in an entire provincial population in Canada. Previously, investigators have reported LABA

monotherapy results as incidental findings.[18,19] For example, Yawn et al[18] investigated charts of 400 randomly-sampled asthma patients from Olmstead County, Minnesota. They found very few patients on LABA monotherapy (n=3). Similarly low numbers were reported by investigators from the United Kingdom, using data from the General Practice Research Database[20]; and by investigators using data from a Medicaid database from Michigan.[21] Although these two studies had large numbers of asthma patients, the prevalence and number of LABA users were quite small in these two jurisdictions (743 and 814 LABA users, respectively). We took a different approach and identified over 50,000 LABA users in British Columbia. This large sample size, covering an entire provincial population, allowed us to identify characteristics of LABA monotherapy among patients already prescribed LABAs, and also included individuals from a broad age range.

Other papers on LABA monotherapy have been randomized clinical trials that have focused on the risks associated with use. Many of these papers included paediatric LABA users in their sample, including children as young as 9 years old. A meta-analysis by Salpeter et al[6] found that the risk of hospitalization was increased in children who took formoterol compared to children on placebo (odds ratio 3.9, 95% confidence interval 1.7 to 8.8), which was similar to the risk found in adults. The FDA conducted a meta-analysis of 110 studies that evaluated LABAs in approximately 60,000 patients with asthma. They developed a composite endpoint of severe asthma exacerbations (asthma-related death, intubation and hospitalization). Their meta-analysis suggested an increased risk of severe asthma exacerbations in patients using LABAs compared to patients who did not use LABAs, -- with the largest risk difference of 14.83 (95% confidence interval 3.24,26.43) seen in patients who were 4-11 years old. (The FDA report can be found at http://www.fda.gov/ohrms/dockets/ac/cder08.html#PulmonaryAllergy).

In light of this increased risk in children, our finding of LABA monotherapy occurring in children, especially in girls and adolescents, is important and requires further study. The higher rate of LABA monotherapy in older patients also warrants further study. Although most of these patients had COPD, where LABA monotherapy is not contraindicated, there is little data available on the effects of LABA monotherapy in the older adult with COPD. The possible increased risk of pneumonia in patients with COPD who take LABA/ICS combination therapy compared with LABA monotherapy[22] complicates the investigation of LABA monotherapy respiratory-related adverse events. Further research in the use of LABA monotherapy in the older adult with COPD is warranted.

There were a few limitations with this study. First, the most recent data available for researchers from the PharmaNet database is from the year 2004. Previous work in this area has utilized data from 2006-2007, a few years later than our data. It is unknown if the LABA monotherapy rates have changed since 2004, given the continued emphasis by regulatory agencies against its use. As more recent PharmaNet data becomes available to researchers, questions about use over time can be addressed. Second, the PharmaNet database[13] records medications that were prescribed, filled and dispensed, but cannot record whether the medication was actually inhaled. However, the number of patients filling, but not using medication is likely to be small in comparison to the large number of LABA users in the entire respiratory population recorded in the database. Finally, it is difficult to ascertain the medication use in the 'mixed' group. The proportion of paediatric patients receiving a LABA was higher than those receiving ICS for each quarter of the study year, which may indicate that there was some LABA monotherapy use in the Mixed Group. However, LABAs and ICS products are dosed differently, so it is possible that the 1 canister may last longer for one type of product versus another. It is possible that while the medications were dispensed at different times, they were still used concurrently.

In conclusion, LABA monotherapy occurs in both children and adults with asthma. The vast majority of patients received LABAs according to Canadian guidelines, which suggests that overall, physicians are prescribing LABAs appropriately. However, there are still many individuals, including children, who are exposed to LABA monotherapy and may be at risk for serious adverse drug reactions. Measures to reduce this

rate, such as continued surveillance and targeted messaging to physicians and pharmacists, are appropriate to reduce LABA monotherapy use for patients with asthma.

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