AUDIT, RESEARCH AND GUIDELINE UPDATE

Long-acting β-agonist prescribing in people with asthma in primary care

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ABSTRACT

Long-acting β2-agonist (LABA) monotherapy is contraindicated in asthma following reports of serious adverse events. Anonymised Scottish health data were used to determine the prevalence of LABA prescribing and LABA monotherapy (sustained and episodic) in asthma during 2006. Of 73 486 asthma patients identified, 5592 (7.6%; 95% CI 7.4% to 7.8%) were prescribed LABAs as a separate inhaler of which 991 patients had LABA monotherapy (17.7% (95% CI 16.7% to 18.7%) of patients at risk). Asthma reviews were associated with reductions in sustained (OR 0.44; 95% CI 0.32 to 0.61) but not episodic monotherapy (OR 1.16; 95% CI 0.85 to 1.57). These findings support recent changes in UK asthma guidelines recommending LABAs in fixed-dose combination inhalers.

INTRODUCTION

Inhaled long-acting β2 agonists (LABAs) produce clinical benefits through sustained bronchodilation in patients with asthma not sufficiently controlled by inhaled corticosteroids (ICS). However, reports of death and serious adverse events in patients treated with LABAs, especially without background ICS therapy, have raised concerns over their safety in chronic asthma management.[1] UK and international guidelines recommend a stepwise approach to asthma management, with LABAs reserved as step three therapy in combination with ICS.[2] Despite safety concerns, there are relatively few data on how common LABA use is in people with asthma. The aim of this study was to investigate how frequently LABAs and LABA monotherapy are prescribed in asthma and which patients receive high-risk LABA monotherapy.

METHODS

This observational study used anonymised data held by the Primary Care Clinical Informatics Unit, University of Aberdeen extracted from 315 Scottish general practices covering approximately one-third of the Scottish population. To access healthcare services provided by the UK National Health Service (NHS), patients routinely register with a general practice. Participating practices all used electronic medical records for registration, morbidity recording and prescribing. Analysis was based on complete data as at 31 March 2007 with asthma defined using UK Quality and Outcomes Framework (QOF) read code sets.[3] The QOF is an NHS national pay-for-performance programme that incentivises practices to create disease registers using electronic read coding systems. Anonymous use of these data has previously been approved by a NHS National Research Ethics Service.

Patient population

Clinical data including age, sex, smoking status, postcode assigned deprivation based upon census and other routine data (using the Carstairs score grouped into fifths) and the presence of a primary care asthma review since 1 January 2005 were extracted for all patients aged ≥5 years with QOF-defined active asthma and no QOF-defined chronic obstructive pulmonary disease (COPD). Primary care asthma reviews are indicated by QOF and gather information on asthma control and clinical management. Data for asthma medications prescribed from 1 April 2005 to 31 March 2007 were obtained. To reduce misclassification of COPD, patients aged ≥40 years were included if they had never smoked.

Practice population

Practice data consisted of remoteness (using the Scottish Executive Urban–Rural Classification), list size (grouped into quarters), whether practices were accredited for post-graduate general practitioner training or dispensed drugs that it prescribed (meaning prescribing choices directly affect practice income), were single handed, achieved maximum points for three relevant QOF measures (medicines 10, when practices receive payment for delivering three prescribing improvement projects, and medicines 11 and 12, when practices are paid for performing annual medication reviews for patients receiving chronic medication) or held a new General Medical Services (nGMS) or section 17c/2c contract (Scottish equivalent of an English Personal Medical Services (PMS) contract). nGMS is the standard, national NHS contract for practices, whereas PMS contracts have local variation.

LABA prescribing

The period prevalence of LABA prescribing (salmeterol or formoterol) was calculated for 2006, including whether LABA prescribing represented sustained or episodic monotherapy. Sustained monotherapy was defined as patients with at least one LABA prescribed as a separate inhaler without any ICS prescription during 2006. Episodic LABA monotherapy was defined as patients with at least one LABA prescribed as a separate inhaler without any ICS prescription within the period 12 weeks before and 8 weeks after the LABA prescription. The presence of episodic monotherapy was calculated for every LABA prescribed as a separate

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inhaler during 2006. Prescriptions for the last 12 weeks of 2005 and the first 8 weeks of 2007 were used to ensure complete ascertainment of ICS exposure for all LABA prescriptions in 2006. ICS and LABA were additionally measured for 2006 using counts of original packets (medicine issued in standard packets produced by the manufacturer; in this case one canister or a 15-disk refill pack).

Data analysis

The prevalence of LABA prescribing was determined by dividing the number of patients prescribed a LABA in the year by the total asthma population. The prevalence of LABA monotherapy among the population at risk (patients prescribed a LABA as a separate inhaler) was determined by dividing the number of patients receiving monotherapy in the year by the total population at risk of monotherapy. The mean number of original packets of ICS and LABA prescribed during 2006 was calculated for those with and without monotherapy.

To assess whether LABA monotherapy varied in association with patient and practice characteristics, two-level multilevel logistic regression was used to account for clustering of patients within practices. The intraclass correlation coefficient (ICC) from the empty model was used to estimate the proportion of variation attributable to practices. Multilevel univariate OR were estimated and a multivariate (adjusted) model then fitted with variables retained based on statistical significance using the Akaike Information Criterion. Descriptive analysis was carried out using SPSS V.18.0 and multilevel logistic regression using STATA V.11.

RESULTS

Of 73 486 patients with asthma, 21 284 (29.0%; 95% CI 28.6% to 29.3%) were prescribed at least one LABA during the calendar year. A total of 15 692 patients (21.4%; 95% CI 21.1% to 21.7%) were prescribed LABAs in a fixed-dose combination only, 4675 (6.4%; 95% CI 6.2% to 6.5%) as a separate

Table 1 Annual prevalence of sustained and episodic LABA monotherapy among the population at risk (n=5592 patients receiving a separate LABA inhaler) including odds ratios from multilevel logistic regression analysis

Variable (no. of patients)	Sustained monotherapy (n=324)			Episodic monotherapy (n=667)		
	Prevalence (%)	Univariate OR (95% CI)	Multivariate OR (95% CI)	Prevalence (%)	Univariate OR (95% CI)	Multivariate OR (95% CI)
Patient level						
Age (years)						
5–11 (455)	3.3	0.49 (0.27 to 0.91)	–	10.5	0.98 (0.67 to 1.44)	–
12–17 (579)	6.2	0.97 (0.61 to 1.54)	–	10.9	1.05 (0.74 to 1.50)	–
18–29 (736)	6.3	1.00	–	10.5	1.00	–
30–39 (942)	7.7	1.26 (0.85 to 1.87)	–	12.4	1.24 (0.91 to 1.69)	–
40–49 (815)	4.5	0.71 (0.45 to 1.12)	–	12.1	1.16 (0.84 to 1.59)	–
50–59 (721)	6.4	1.08 (0.70 to 1.67)	–	14.6	1.47 (1.07–2.02)	–
60–69 (614)	4.7	0.78 (0.48 to 1.27)	–	12.7	1.22 (0.87 to 1.71)	–
≥70 (730)	5.8	0.92 (0.59 to 1.44)	–	11.0	1.04 (0.75 to 1.46)	–
Sex						
Men (2124)	6.1	1.00	–	12.7	1.00	–
Women (3468)	5.6	0.91 (0.72 to 1.15)	–	11.4	0.88 (0.75 to 1.04)	–
Deprivation						
1 affluent (981)	5.8	1.00	–	15.0	1.00	1.00
2 (1275)	5.6	0.87 (0.58 to 1.30)	–	11.5	0.73 (0.57 to 0.94)	0.74 (0.58 to 0.96)
3 (1351)	6.4	1.02 (0.68 to 1.54)	–	12.0	0.78 (0.61 to 1.01)	0.78 (0.61 to 1.00)
4 (1009)	5.4	0.77 (0.49 to 1.19)	–	12.1	0.76 (0.58 to 1.00)	0.75 (0.58 to 0.99)
5 deprived (976)	5.6	0.79 (0.51 to 1.24)	–	9.1	0.56 (0.42 to 0.74)	0.56 (0.42 to 0.75)
Asthma review						
Not reviewed (509)	11.2	1.00	1.00	10.0	1.00	–
Reviewed (5083)	5.3	0.44 (0.32 to 0.60)	0.44 (0.32 to 0.61)	12.1	1.16 (0.85 to 1.57)	–
Practice level						
Dispensing						
No (5331)	5.7	1.00	–	12.2	1.00	1.00
Yes (222)	8.1	1.47 (0.80 to 2.69)	–	6.8	0.54 (0.31 to 0.92)	0.52 (0.30 to 0.90)
Contract						
nGMS (5046)	5.5	1.00	1.00	11.8	1.00	–
2c or 17c (507)	8.9	1.51 (0.95 to 2.40)	1.47 (0.92 to 2.34)	13.2	1.17 (0.88 to 1.56)	–
Single handed						
No (5425)	5.8	1.00	–	12.0	1.00	1.00
Yes (128)	7.8	1.44 (0.67 to 3.09)	–	8.6	0.70 (0.37 to 1.33)	0.77 (0.41 to 1.46)

There were no significant differences in the following practice characteristics with either sustained or episodic monotherapy: list size, post-graduate training status, maximum points for quality and outcomes framework medicines 10, 11 and 12, and remoteness. Contract status was non-significant following adjusted analysis of sustained monotherapy but was included in the final model due to improved model fit. Singled handed practice was non-significant following adjusted analysis of episodic monotherapy but was included in the final model due to improved model fit.
LABA, long-acting β2 agonist; nGMS, new General Medical Services.

LABA inhaler only and 917 (1.3%; 95% CI 1.2% to 1.3%) received both.

Among the 5592 patients prescribed a LABA as a separate inhaler (the population at risk of LABA monotherapy), 991 had LABA monotherapy (17.7% (95% CI 16.7% to 18.7%) of patients at risk, 1.4% (95% CI 1.3% to 1.4%) of all patients with asthma). Sustained LABA monotherapy occurred in 324 patients (5.8% (95% CI 5.2% to 6.4%) of patients at risk, 0.4% (95% CI 0.4% to 0.5%) of all patients with asthma) with episodic monotherapy occurring in an additional 667 patients (11.9% (95% CI 11.1% to 12.8%) of patients at risk, 0.9% (95% CI 0.8% to 1.0%) of all asthma patients).

Characteristics associated with LABA prescribing and LABA monotherapy

The prevalence of LABA prescribing increased steadily with age, being highest in patients over the age of 60 (see online supplementary table S1). Young children were less likely to be prescribed LABAs in a fixed-dose combination with ICS (9.5% for children aged 5–11 vs 20.0% for adults aged 18–29, difference 10.5%; 95% CI 9.1% to 11.7%). LABAs were more likely to be prescribed in women, although absolute differences were small.

The prevalence of sustained and episodic LABA monotherapy is shown in table 1. Among patients prescribed LABAs as a separate inhaler, the prevalence of sustained monotherapy was lower in those with a primary care asthma review (5.3% vs 11.2% without review; adjusted OR 0.44; 95% CI 0.32 to 0.61). Episodic monotherapy was less common in deprived patients (9.1% vs 15.0% for the most affluent; adjusted OR 0.56; 95% CI 0.42 to 0.76) and among dispensing practices (6.8% vs 12.0% for non-dispensing practices; adjusted OR 0.52; 95% CI 0.30 to 0.90). No other patient or practice variables were significantly associated with episodic monotherapy, including primary care asthma reviews. The ICC was 0.127 for sustained LABA monotherapy and 0.012 for episodic monotherapy, indicating that differences between practices contributed little to the variation in episodic monotherapy.

Patients with episodic monotherapy received significantly less original packets of ICS during 2006 than patients prescribed LABA as a separate inhaler without monotherapy (4.0 op vs 7.5 op respectively; mean difference 3.6 op; 95% CI 3.2 to 4.0) despite receiving similar numbers of LABAs (see online supplementary table S2).

DISCUSSION

Reports of asthma deaths and serious adverse events resulted in US Food and Drug Administration and UK Medicines and Healthcare Products Regulatory Agency advice highlighting potential risks with LABA monotherapy, with pre-2006 guideline recommendations that LABAs only be used in conjunction with ICS in people with asthma.[1] In this study, LABA monotherapy was rare in that only 1.3% of all people with asthma were affected, partly because only 7.6% of people with asthma were prescribed LABA as a separate inhaler. However, among the population at risk (patients prescribed LABA as a separate inhaler), LABA monotherapy occurred in 17.7% of patients. Among different patient and practice characteristics investigated, primary care asthma reviews were significantly associated with lower rates of sustained LABA monotherapy but not episodic monotherapy.

Relatively little detailed published information regarding the extent of LABA monotherapy in routine clinical practice exists. One smaller US study investigating LABA monotherapy among people with asthma reported a prevalence of 11% during 2006 using a definition similar to our measure for sustained monotherapy.[4] However, in our study episodic monotherapy was more significant probably as a result of non-adherence with ICS which is supported by this group receiving significantly less ICS throughout the year. Differential non-compliance could occur if symptoms develop sooner when discontinuing LABA compared with ICS and may lead to treatment failure within 8 weeks of LABA monotherapy.[5]

In June 2011, revised UK national asthma guidelines recommended that LABAs only be prescribed in fixed-dose combination with ICS, to improve adherence and reduce the risk of LABA monotherapy. However, the extent to which monotherapy actually occurred was uncertain. This study shows that although LABA monotherapy was relatively uncommon among the entire asthma population, it commonly occurred in people treated with separate inhalers. Attending an asthma review was associated with lower rates of sustained but not episodic LABA monotherapy which occurred more commonly. These findings support recent changes in UK asthma guidelines recommending LABAs only be used in fixed-dose combination inhalers to prevent LABA monotherapy.

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