

Differences in physicians' self-reported knowledge of, attitudes toward, and responses to the black box warning on long-acting β -agonists

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Background: Inhaled corticosteroids and long-acting β -agonists (LABAs) are recommended for treating moderate to severe persistent asthma. The Food and Drug Administration has issued a black box warning (BBW) for LABAs.

Objective: To investigate physician knowledge of the BBW and its effect on the practice of specialists (pulmonologists and allergists) and primary care physicians (PCPs) (internists and family physicians).

Methods: A total of 1,107 physicians responded to a questionnaire to determine their awareness of the BBW and whether it changed their practice.

Results: The group comprised 429 pulmonologists (38.8%), 395 allergists (35.7%), 141 internists (12.7%), 132 family physicians (11.9%), and 10 pediatricians (0.9%). Comparing specialists with PCPs, there was approximately a 10% difference in the rate of knowledge concerning the BBW (99.0% vs 90.8%, $P < .001$). Approximately a quarter of specialists agreed with the BBW compared with 52.9% of family physicians and 40.3% of internists. Twice as many PCPs vs specialists agreed with the warning (45.6% vs 24.2%, $P < .001$). The PCPs were more likely to alter their prescribing habits than were specialists (40.1% vs 34.6%, $P < .005$). Specialists were more likely to discuss the warning with patients than were PCPs (87.4% vs 64.8%, $P < .001$). For mild persistent asthma, most respondents chose inhaled corticosteroids as the preferred first-line therapy, but 11.4% of PCPs and 2.1% of specialists identified LABA monotherapy as their first choice. For moderate to severe asthma, the pattern of response was similar.

Conclusion: Although most physicians were aware of the BBW for LABAs, there was a difference in how specialists and PCPs approached it and altered their prescribing habits.

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INTRODUCTION

For the treatment of moderate to severe persistent asthma, national and international guidelines^{1,2} recommend the combination of inhaled corticosteroids (ICSs) and long-acting β -agonists (LABAs) to achieve appropriate asthma control. However, as of November 18, 2005, the federal Food and Drug Administration (FDA) placed a black box warning (BBW) on all LABAs and products that contain the combination of an ICS and a LABA.³ The BBW appears in the package insert for prescription drugs that may cause serious adverse effects. For asthmatic patients who are prescribed LABAs, the BBW was issued after a review of unpublished and published data on salmeterol

and formoterol. The two published studies suggesting that LABAs were associated with increased mortality in asthmatic patients include the Serevent Nationwide Surveillance Study⁴ and the Salmeterol Multicenter Asthma Research Trial (SMART).⁵ However, the BBW was issued largely due to the SMART.

The SMART, sponsored by GlaxoSmithKline (Research Triangle Park, North Carolina), was designed to evaluate the effect of LABAs on approximately 60,000 asthmatic patients who were naive to the drug.⁵ Participants were provided with a 6-month supply of salmeterol or placebo and were then contacted monthly by telephone to determine whether they had experienced a life-threatening asthma exacerbation. An interim analysis revealed an increase in asthma mortality rates, particularly in the subgroup of African-American patients. Criticism of this study has been based on several issues. Specifically, investigators obtained minimal demographic information, including the use of controller medications. Measurement of lung function was not required, no interim study visits other than the telephone contact were conducted, and compliance was not measured. Despite these study limitations, the FDA instituted a BBW.

The previous literature demonstrated that LABAs are corticosteroid sparing^{4–7} and that asthma control is supe-

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rior with combined ICS-LABA treatment compared with increasing the dose of ICS.⁸ In addition, the use of LABAs as monotherapy has been reported to be associated with an increase in asthma exacerbation rates, and it was postulated that this finding might be due to masking underlying inflammation.^{7,9} This literature and many other studies established the basis of the current asthma treatment guidelines regarding the use of LABAs in asthma.^{1,2} Thus, consideration must be given to safety issues and evaluation of asthma control when prescribing LABAs combined with an ICS for asthmatic patients. The FDA has not clearly indicated how physicians should proceed with this warning for asthmatic patients and how to communicate this information to them. As such, physicians are confronted with the dilemma of deciding how to interpret this literature and apply it to their clinical practice. It has been suggested that the approach to this clinical issue might vary depending on medical subspecialty training and background. Before this article, Oppenheimer and Aaronson¹⁰ reported the results of a questionnaire from the Joint Council of Allergy, which found that 51% of allergists reduced their use of LABAs or ICS-LABA combination products because of the BBW. The effect on other groups of physicians was not addressed in their survey. We developed and distributed a survey through the American College of Chest Physicians (ACCP) to ascertain how the BBW has been perceived by specialty physicians (pulmonologists and allergists) and by primary care physicians (PCPs) (internists and family physicians) and how it has affected their clinical practice. We now report on the largest survey to date to investigate practice patterns in multiple physician groups and how these groups compare in their approach to this important clinical issue.

METHODS

An online computerized questionnaire using SurveyMonkey software was developed by the Airways Disorders Steering Committee of the ACCP (Fig 1) and was distributed via e-mail to members of the ACCP, the American Academy of Allergy, Asthma, and Immunology, the American Academy of Family Practice, and the American College of Physicians. This survey gathered responses from a sample of physicians regarding (1) their awareness of and attitudes toward the BBW and SMART, (2) whether the BBW altered their clinical practice, and (3) whether they initiated discussions with their patients about the warning. In addition, their overall choices of medications for various categories of persistent asthma were explored.

All responses to the survey were in the form of categorical variables. Data are presented as numbers (percentages). Relationships between variables were evaluated using Pearson χ^2 tests or Fisher exact tests. All the analyses were conducted using a software program (STATA version 10; StataCorp LP, College Station, Texas).

RESULTS

Physician Groups

A total of 11,147 questionnaires were sent to physicians, and 1,107 responses (9.9%) were received (20% response rate for pulmonologists, 13% for allergists, 5% for internists, and 4% for family physicians). Respondents consisted of 429 pulmonologists (38.8% of all respondents), 395 allergists (35.7%), 141 internists (12.7%), 132 family physicians (11.9%), and 10 pediatricians (0.9%). Because there was such a small response from pediatricians, we did not analyze this subgroup independently. For the entire sample, 64.4% were in private practice, 24.1% were in academic practice, 4.8% were in training programs, and 6.6% were in other settings (ie, clinic groups, military, or hospitalists).

Awareness of the BBW and Practice Pattern Changes

Ninety-seven percent of the physicians surveyed were aware of the BBW. Figure 2 shows the differences across specialties, ranging from a high of 100% awareness among allergists to 87.8% awareness among physicians practicing internal medicine. There was approximately a 10% difference in the self-reported rate of awareness of the BBW among pulmonologists and allergists vs PCPs (99.0% vs 90.8%, $P < .001$). There was wide variation in the degree to which physicians of various specialties agreed or disagreed with the warning. Overall, approximately half of the physicians surveyed (50.6%) did not agree with the BBW, 29.5% agreed, and 19.9% were not sure. The rates of agreement with the warning were higher in PCPs than in specialists (Table 1). Approximately one-quarter of specialists (23.1% of allergists and 25.2% of pulmonologists) agreed with the BBW, whereas 52.9% of family physicians and 40.3% of internists agreed with the warning. Overall, approximately twice as many PCPs agreed with the warning compared with specialists (45.6% vs 24.2%; $P < .001$).

As with the BBW, most physicians were familiar with SMART: 57% reported being very familiar, 28% somewhat familiar, and 14% not familiar with SMART. Figure 3 shows the percentage of responding physicians who reported each level of familiarity. Most specialists reported being very familiar with SMART, but few family practitioners responded similarly.

Most physicians did not change their practice patterns for treating asthma (Table 2). Specifically, 62.6% of specialists and 53.8% of PCPs did not alter their practice patterns. However, PCPs were 6% more likely to have altered their practice patterns compared with specialists ($P = .005$). When treating patients with chronic obstructive pulmonary disease, PCPs were nearly twice as likely as specialists to have changed their practice patterns ($P < .001$). For African-American asthmatic patients, however, PCPs were half as likely as specialists to have changed their practice patterns (17.2% vs 35.1%, $P < .001$).

Survey for Allergists, Family Practitioners, Internists, and Pulmonologists: Use of Long-Acting Beta-Agonists

1. Select your primary specialty from the following list. *Please choose one.*
Pulmonology
Family Practice
Internal Medicine
Allergy
Pediatrics
2. Area of practice: *Please choose one.*
I am in private practice
I am in academic practice
I am in training
Other. *Please specify:* _____
3. Are you aware of the FDA black box warning for Serevent, Foradil, and Advair?
Please choose one.

Yes**No**
4. Do you agree with the FDA black box warnings? *Please choose one.*

Yes**No****Not sure**
5. Have you ever initiated a discussion of the FDA black box warning with your patients? *Please choose one.*

Yes**No**

If yes, do you always discuss the black box warning, sometimes discuss it, or seldom discuss it? *Please choose one.*

Always**Sometimes****Seldom**
6. Has the discussion of the FDA black box warnings ever been initiated by your patient? *Please choose one.*

Yes**No**
7. Are you familiar with the SMART study (Salmeterol Multicenter Asthma Research Trial: A Comparison of Usual Pharmacotherapy for Asthma or usual pharmacotherapy Plus Salmeterol)? *Please choose one.*

Very**Somewhat****Not familiar**
8. Have you changed your treatment regimen for asthma based on the black box warning? *Please choose one.*

Yes**No****Not sure**

Figure 1. Survey instrument. FDA indicates Food and Drug Administration; COPD, chronic obstructive pulmonary disease.

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9. Has the SMART study changed your prescribing habits concerning your African-American patients? *Please choose one.*

Yes No Not sure

- 10A. For **mild persistent asthma**, in what order do you usually prescribe the controller medications listed below? *Please choose first; second; or third, next to each controller medication.*

Inhaled Corticosteroids	First	Second	Third
Long-acting Beta-agonist	First	Second	Third
Leukotriene Modifier	First	Second	Third

- 10B. For **moderate and severe persistent asthma**, in what order do you usually prescribe the controller medications listed below? *Please choose first; second; or third, next to each controller medication.*

Inhaled Corticosteroids	First	Second	Third
Long-acting Beta-agonist	First	Second	Third
Leukotriene Modifier	First	Second	Third

11. Have you changed your treatment of COPD based on the black box warning? *Please choose one.*

Yes No I do not see patients with COPD

Figure 1. Continued.

Discussions With Patients

Although slightly more than 80% of all physicians indicated that they discussed the BBW with their patients, specialists were more likely to do so (87.4% of specialists vs 64.8% of PCPs, $P < .001$). In particular, allergists and pulmonologists were significantly more likely to report that they initiate discussions with their patients (Fig 2). Specialists also reported that their patients were twice as likely to initiate a discussion of the BBW compared with PCPs (70.3% vs 32.5%, $P < .001$).

Asthma Treatment

For mild persistent asthma, most respondents chose ICSs as the preferred first-line therapy, regardless of specialty. Among PCPs, 11.4% of respondents indicated that LABA monotherapy was their first choice. In contrast, 2.1% of specialists identified LABA monotherapy as a first choice ($P < .001$). Pulmonologists were somewhat less likely than others to report using leukotriene modifiers as a first-line therapy (3.3% vs 9%–13%). For moderate to

severe persistent asthma, the pattern of response was similar (Fig 4).

DISCUSSION

In this large, self-reported survey, although most physicians were aware of the BBW for LABAs, specialists were significantly more aware of it than were PCPs. Furthermore, among physicians who were aware of the warning, PCPs agreed with it twice as often as did specialists. Although approximately one-third of physicians changed their practice patterns, it was more frequent for PCPs to do so than for specialists. The exception was regarding African-American patients, whereby specialists were twice as likely to change their management. The 2 specialty groups (allergists and pulmonologists) did not differ in the rate at which they altered their practice patterns. Specialists tended to discuss the warning with their patients more often than did PCPs, with allergists initiating the most discussions. For chronic obstructive pulmonary disease, where the BBW does not apply but LABAs are frequently prescribed, the practice patterns were not altered for special-

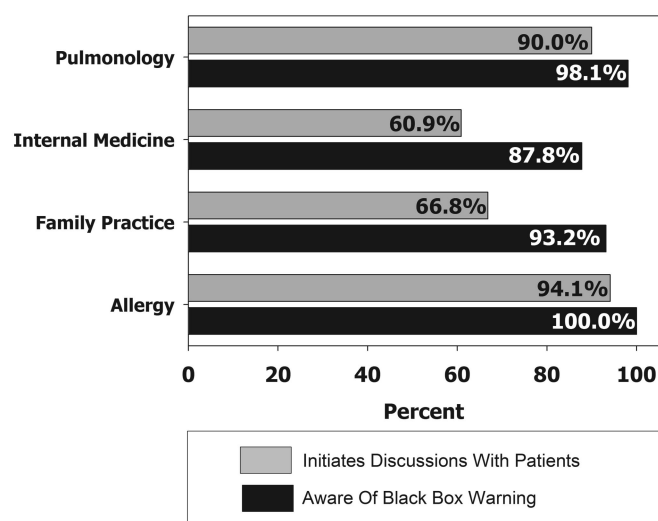


Figure 2. Percentage of physicians who are aware of the Food and Drug Administration black box warning and who initiate discussions with patients, by specialty.

ists, but PCPs were twice as likely to alter their prescribing patterns.

In keeping with asthma guidelines,¹ most physicians selected ICSs as the first treatment of choice. Of importance, a few PCPs chose LABAs as their initial asthma treatment.

The findings from this survey suggest that physicians are largely aware of the BBW for LABAs, but there are differences in how this is translated into clinical practice by different physician groups. The reasons for this may reflect different interpretations of the literature or possibly different emphasis by their supporting societies. One might speculate that specialists have spent more time reviewing and discussing these issues among themselves and their specialty societies than have PCPs. This may be the explanation as to why specialists have altered their prescribing habits for African-American asthmatic patients more often than have PCPs. Specialty physicians may be more aware of genetic polymorphisms that were initially reported to be associated with poorer outcomes in certain African-American individuals at the time of this survey.¹¹ This relationship, however, has more recently been questioned.¹²

Differences in awareness of the literature might also explain why PCPs indicated that they altered their prescribing habits for patients with chronic obstructive pulmonary disease, where the BBW does not apply. Thus, differences in practice patterns may be reflected in the “company” physicians keep. It is disturbing that more than 10% of PCPs indicated that they prescribe LABAs as monotherapy. This is important because, as previously noted, several studies^{6,8,13} have demonstrated that there is an increase in exacerbation rates when using LABAs as monotherapy. This is best demonstrated in the Salmeterol

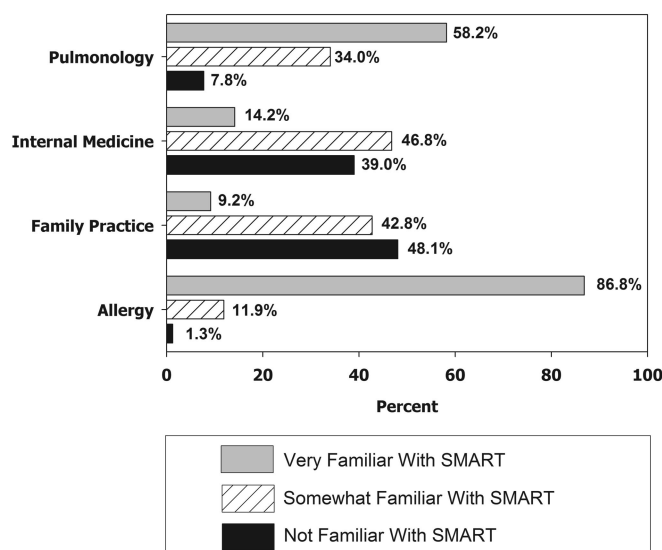
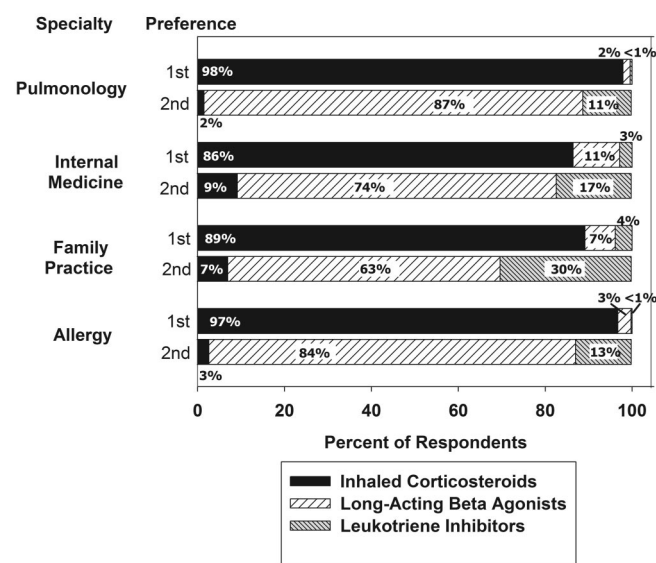


Figure 3. Familiarity of physicians with the Salmeterol Multicenter Asthma Research Trial (SMART), by specialty.



Differences in drug preference across sub-specialties are significant with $p < 0.001$ for both first and second preference therapies

Figure 4. Physician differences in drug preferences for moderate to severe asthma treatment, by specialty.

or Corticosteroids trial,⁷ in which patients who were well controlled with ICSs were randomized to either continue taking ICSs or receive salmeterol or placebo. The LABA group demonstrated an increase in markers of inflammation and an exacerbation rate similar to that of the placebo group. There was a significant increase in clinically relevant exacerbations when the salmeterol group was compared with the group that continued taking ICSs. However,

Table 1. Agreement With the FDA Black Box Warning by Physician Specialty^a

Response	Physicians, No. (%)			
	Allergy (n = 394)	Family practice (n = 121)	Internal medicine (n = 139)	Pulmonology (n = 424)
Do not agree	239 (60.7)	57 (47.1)	24 (17.3)	224 (52.8)
Not sure	64 (16.2)	0	59 (42.5)	93 (21.9)
Agree	91 (23.1)	64 (52.9)	56 (40.3)	107 (25.2)

Abbreviation: FDA, Food and Drug Administration.

^a $\chi^2_8 = 138.8$ for the difference in agreement across physician specialty ($P < .001$).

Table 2. Whether Physicians Changed Practice Patterns for Treating Asthma and COPD by Specialist and PCP Status^a

Response	Asthma		COPD	
	PCP (n = 279)	Specialist (n = 817)	PCP (n = 262)	Specialist (n = 680)
Did not change practice	150 (53.8)	511 (62.6)	195 (74.4)	582 (85.6)
Changed practice	112 (40.1)	283 (34.6)	67 (25.6)	98 (14.4)
Not sure	17 (6.1)	23 (2.8)	0	0

Abbreviations: COPD, chronic obstructive pulmonary disease; PCP, primary care physician.

^a Data are given as number (percentage). $\chi^2_2 = 10.5$ for difference in changing asthma practice patterns across specialties ($P = .005$); $\chi^2_1 = 16.3$ for difference in changing COPD practice patterns across specialties ($P < .001$).

there is considerable literature^{8,13} demonstrating the safety of LABAs if used in combination with ICSs.

Although noteworthy, the findings of this study are subject to several limitations. One concern is the overall low response rate (10%) to the mailed survey. Although the rate is consistent with that of other surveys of physicians, there may be some selection bias in responses if those who are more familiar with the use of LABAs were more motivated to respond. A second and more significant concern is the much higher response rate from specialists than from generalists. Whereas 1 in 5 pulmonologists responded to the survey, only approximately 1 in 100 PCPs responded. Despite this, the number of responses was still large enough to determine statistically significant differences among the groups. However, owing to the low rate of response, these findings on specialty-related differences in awareness and changes in practice patterns should be treated as tentative.

In summary, this survey of practice patterns of specialists and PCPs regarding the FDA BBW demonstrates that most physician groups were cognizant of the warning but that there are differences as to their agreement with the warning and their perception of how it has affected their respective clinical practices.

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