

Quantifying asthma patient preferences for onset of effect of combination inhaled corticosteroids and long-acting beta₂-agonist maintenance medications

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ABSTRACT

The Onset-of-Effect Questionnaire (OEQ) is a self-administered instrument used to assess patient perception of how quickly asthma maintenance medications begin to work. This study was designed to quantify the relative importance that patients using combination inhaled corticosteroid and long-acting beta₂-agonist (ICS/LABA) maintenance medication place on the onset-of-effect outcomes. Patients aged ≥18 years with a self-reported diagnosis of asthma, currently using combination ICS/LABA maintenance medication, completed an Internet-based SC conjoint survey instrument that included 10 choice trade-off tasks. In four choice tasks, patients were asked to choose between two hypothetical medications. In six choice tasks, patients were asked to choose among two hypothetical medications and their current medication. Each choice alternative was defined by response levels of the five OEQ statements and out-of-pocket cost. We used random-parameters logit methods to estimate the relative importance of outcomes assessed by the OEQ. Five hundred nine patients completed the study. Satisfied was the most important OEQ outcome and physical sensations were the least important. When offered a choice, 80% (95% CI, 75–85%) of patients preferred a maintenance medication for which they are satisfied with how quickly they feel it begins to work and 62% (95% CI: 57–67%) of patients preferred a maintenance medication that they feel begins to work right away. Combination maintenance medications with rapid onset of effect, especially those that impact a patients' ability to feel the medication work right away and patient satisfaction with how quickly the medication works, may increase the use of and adherence to maintenance medications.

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Key words: Asthma, combination therapy, conjoint analysis, discrete choice experiment, inhaled corticosteroid, long-acting beta-adrenergic agonist, maintenance medication, survey, onset of effect, patient preferences

Asthma is a reversible obstructive lung disease caused by increased reaction of the airways to various stimuli. It is a serious chronic medical condition and can be life-threatening if not properly managed. In 2005, the Centers for Disease Control and Prevention estimated that nearly 22 million Americans had asthma and nearly 12 million of these had an attack or episode during the previous year.¹ Asthma patients who have experienced an asthma attack are twice as likely as other patients to experience additional exacerbations.² Despite the availability of many medications in the United States to treat adults with asthma, the disease is still poorly controlled.

Studies have shown that patients experience emergency department visits, hospitalizations, or attacks at a steady rate.^{3–6} The annual direct health care cost of the disease in the United States is approximately \$10 billion. Indirect costs (*e.g.*, lost productivity due to missed days at school or work) add another \$8 billion, for a total cost of \$18 billion/year.⁷

Clinical trials have indicated that the combination of an inhaled corticosteroid (ICS) and a long-acting β₂-agonist (LABA) is an effective long-term maintenance treatment for asthma in patients ≥12 years of age whose asthma is not well controlled on ICS alone.^{8,9} ICS/LABA combination maintenance treatments available in a single inhaler include fluticasone/salmeterol and budesonide/formoterol. The two single-inhaler combination maintenance treatments differ in the onset of bronchodilation caused by the LABAs, with formoterol having a more rapid onset than salmeterol.

The Onset-of-Effect Questionnaire (OEQ) is a validated self-administered instrument used to assess patient perception of how quickly asthma maintenance medications begin to work.^{10,11} The OEQ elicits patient ratings for five statements: “I could tell the medication was working” (Medication Works); “I could feel the

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medication begin to work right away" (Works Right Away); "I felt physical sensations shortly after taking the medication that reassured me it was working" (Physical Sensations); "The medication worked as quickly as my rescue medication" (Rescue); and "I was satisfied with how quickly I felt the medication begin to work" (Satisfied). In the OEQ, patients are asked to indicate their agreement with each statement using a Likert scale that includes the following five levels: strongly agree, somewhat agree, neither agree nor disagree, somewhat disagree, and strongly disagree.

Two large placebo-controlled clinical trials were conducted that included assessments of two prespecified OEQ end points: item 2, "I could feel the medication begin to work right away" (Works Right Away); and item 5, "I was satisfied with how quickly I felt the medication begin to work" (Satisfied).¹² In both of these trials, significantly more patients receiving budesonide/formoterol pressurized metered-dose inhaler (pMDI) 80/4.5 μg and 160/4.5 μg $\times 2$ actuations twice daily reported feeling their medication begin to work right away as well as satisfaction with how quickly they felt it begin to work compared with budesonide hydrofluoroalkane pMDI 80 μg and 160 μg $\times 2$ actuations twice daily as measured by the OEQ.¹²

The objective of this study was to quantify the relative importance that patients using combination ICS/LABA maintenance treatment place on the five outcomes assessed by the OEQ. Of particular interest was the importance of each of the two end points measured in recent clinical trials—Works Right Away and Satisfied—relative to each other and to the other three outcomes in the OEQ. To accomplish this objective, we surveyed asthma patients in the United States who use ICS/LABA combination maintenance medications using an Internet-based stated-choice (SC) conjoint questionnaire.

METHODS

Survey Instrument

SC conjoint survey methods—also known as discrete-choice experiments—have been widely used and validated in marketing research, transportation, and environmental economics.^{13–17} SC is a systematic method of eliciting trade-offs to quantify the relative importance patients (or physicians or other health care decision makers) assign to various treatment attributes or outcomes. It is based on the premise that medical interventions are composed of a set of attributes or outcomes and that the attractiveness of a particular intervention to an individual is a function of these attributes.¹⁸ These methods are increasingly used in health economics to estimate patients' and physicians' stated preferences for health care interventions, treat-

ment alternatives, and health care services (see Ref. 19 for a recent review of SC conjoint applications in health.) These methods are appropriate when the research objective is to estimate patient preferences over a wide range of outcomes or end points that cannot be observed in clinical or observational trials.

In an SC survey, subjects are asked to complete a series of choice tasks. In each choice task a subject is asked to indicate which of two or more treatment alternatives he or she prefers. Each treatment alternative is defined by a set of hypothetical treatment attributes or outcomes and the levels of these outcomes vary between alternatives and across choice tasks according to an experimental design with known statistical properties. By observing the pattern of choices subjects make in different choice tasks, we can quantify the relative importance of each treatment attribute as well as the relative importance of changes in the levels of each treatment attribute.

Six attributes were selected to describe asthma maintenance treatment alternatives in this study. These include the level of agreement with each of the five OEQ statements plus monthly out-of-pocket costs (Table 1). In each of the first four choice tasks, patients currently using combination ICS/LABA maintenance treatments were asked to choose between two hypothetical maintenance treatment alternatives (Fig. 1). In six subsequent choice tasks, patients were asked to choose among two hypothetical maintenance treatments and their current maintenance treatment (Fig. 2). In addition, the SC survey elicited standard demographic information (*e.g.*, age, gender, education, and race) as well as a number of items about the patients' experience with asthma and asthma medications.

The current-treatment alternative was included to control for a patient's treatment experience. The five OEQ statements were presented before the choice questions, and patients were asked to select the response that best described the extent to which they agreed or disagreed with each statement about their experience with their current ICS/LABA combination maintenance treatment during the past week. Subjects' responses to these five statements were used to construct the current-treatment alternative in the three-alternative choice tasks.

To create treatment profiles for the choice tasks, we used a variation of a commonly used algorithm to construct an experimental design resulting in 32 choice pairs.^{20–24} The final experimental design consisted of four survey versions or blocks, each containing eight choice pairs. Each patient was randomly assigned to one of the four blocks. After completing eight choice tasks from a design block (four two-alternative tasks and four three-alternative tasks), two of the four two-alternative choice tasks were randomly repeated as three-alternative choice tasks by adding the current-

Table 1 Attributes and levels

Medication Attribute	Choice Task Description	Abbreviated Label	Levels
Statement 1—During the past week, you could tell that your maintenance medication was working	I could tell that the medication worked	Medication works	Strongly <u>agree</u> Neither Strongly <u>disagree</u>
Statement 2—During the past week, you could feel your maintenance medication begin to work right away	I could feel the medication begin to work right away	Works right away	Strongly <u>agree</u> Neither Strongly <u>disagree</u>
Statement 3—During the past week, you felt physical sensations shortly after taking your maintenance medication that reassured you that it was working	I felt physical sensations shortly after taking the medication that reassured me that it was working	Physical sensations	Strongly <u>agree</u> Neither Strongly <u>disagree</u>
Statement 4—During the past week, your maintenance medication worked as quickly as your rescue medication	The medication worked as quickly as my rescue medication	Rescue	Strongly <u>agree</u> Neither Strongly <u>disagree</u>
Statement 5—During the past week, you were satisfied with how quickly you felt your maintenance medication begin to work	I was satisfied with how quickly I felt the medication begin to work	Satisfied	Strongly <u>agree</u> Neither Strongly <u>disagree</u>
Monthly out-of-pocket costs of the medication	Monthly out-of-pocket costs of the medication	Cost	\$35 \$40 \$50 \$70

treatment alternative. Thus, each subject was presented with a total of 10 choice tasks. The survey was approved by RTI International's Office of Research Protection and Ethics (Research Triangle Park, NC).

Survey Sample

All patients were required to have a self-reported physician-made diagnosis of asthma, currently using prescription ICS/LABA combination maintenance medication(s) (either a fixed-dose combination product or a combination of ICS and LABA taken with separate devices), and be a U.S. resident ≥ 18 years of age. All patients provided informed consent to participate in this study.

Knowledge Networks (KN) recruited members from its existing online panel and administered the survey in October 2007. Members of the KN panel are recruited through random-digit dialing and are provided with equipment for receiving Internet-based surveys if they do not have Internet access at home. The KN panel provides a well-documented method for con-

ducting Internet-based survey research with a nationally representative probability sample.^{25,26} The KN panel represents the broad diversity and key demographic dimensions of the U.S. population. The panel closely corresponds to the U.S. population on age, race, Hispanic ethnicity, geographic region, employment status, and other demographic elements.

Statistical Analysis

We used multivariate, random parameters or mixed-logit regression to estimate importance weights for each treatment attribute and treatment attribute level presented in Table 1 and to predict treatment choices among pairs of hypothetical treatment profiles. In random-parameters logit, the independent variable is treatment choice and a regression equation is used to estimate the effect of each attribute level on the probability of choosing a treatment alternative. Thus, logit allows us to estimate a unique coefficient for each attribute level. Each estimated coefficient represents

People like you said the following when taking the maintenance medications presented below:

During the past week...	Medication A	Medication B
I could tell that the medication worked	Strongly <u>agree</u>	Strongly <u>agree</u>
I could feel the medication begin to work right away	Strongly <u>agree</u>	Neither agree nor disagree
I felt physical sensations shortly after taking the medication that reassured me that it was working	Strongly <u>agree</u>	Strongly <u>disagree</u>
The medication worked as quickly as my rescue medication	Strongly <u>agree</u>	Strongly <u>agree</u>
I was satisfied with how quickly I felt the medication begin to work	Strongly <u>agree</u>	Strongly <u>agree</u>
Monthly out-of-pocket cost of the medication	\$40	\$35
Which medication would you choose if these were your only options?	☐	☐

Next

Figure 1. Patient choice between two hypothetical maintenance treatments.

the importance of the corresponding attribute level to treatment choice.

Random-parameters logit avoids potential estimation bias from unobserved preference heterogeneity in discrete-choice models by estimating a distribution of preferences across patients for each preference parameter.^{27,28} In addition, because each subject provided responses to more than one choice question, we estimated a random-effects panel model to account for within-subject correlation.

The scale on which the coefficients are estimated has no direct interpretation and can include both positive and negative values. Thus, the importance of one treatment feature is best understood relative to the importance of another treatment feature. To compare the relative importance of treatment attributes in this study, we assigned a value of 10 to the most important treatment attribute; *i.e.*, we rescaled the coefficient on “strongly disagree” for the most important attribute to equal 0 and the coefficient on “strongly agree” for the most importance attribute to equal 10. The estimated coefficient for each of the remaining attribute levels was then rescaled between these extremes. Thus, the size of the importance weight represents the relative importance of each OEQ treatment outcome relative to the most important OEQ treatment outcome.

Predicted preferences for treatments with different levels of OEQ outcomes were derived directly from the random-parameters model estimates. We conducted split-sample analyses according to age, education, gender, race, type of asthma medication, duration of asthma, and severity of symptoms. All statistical analyses were conducted using GAUSS 8.0 (Aptech Systems, Inc., Black Diamond, WA).

RESULTS

Patient Sample

KN sent E-mail invitations to 1855 potential members of its panel with a self-reported diagnosis of asthma; 518 (28%) patients met the inclusion criteria for the study and 509 (98%) patients consented to participate. Table 2 presents the demographic characteristics of qualified patients who completed the survey instrument. Of the 509 patients in the final sample, only 2.2% had one or more missing responses for the choice tasks. The assignment of patients to each of the four design blocks was fairly uniform and ranged between 23.4 and 26.7% of the sample.

Relative Importance of OEQ Outcomes

The OEQ outcome that was most important to patients in this study was “I was satisfied with how quickly I felt the medication begin to work” (Satisfied), with a mean relative importance weight of 10.0 ($p < 0.0001$). The second and third most important attributes were “I could tell the medication was working” (Medication Works), with a mean relative importance weight of 7.5 ($p < 0.0001$), and “I could feel the medication begin to work right away” (Works Right Away), with a mean relative importance weight of 3.5 ($p < 0.0001$). The difference in importance between the Satisfied and Medication Works attributes was not statistically significant at the 5% level; however, both the Satisfied and the Medication Works attributes were statistically significantly more important than the Works Right Away attribute at the 5% level. The least important attributes were “I felt physical sensations shortly after taking the medication that reassured me it

People like you said the following when taking the maintenance medications presented below:

During the past week...	Medication A	Medication B	Your Current Medication
I could tell that the medication worked	Neither agree nor disagree	Strongly <u>agree</u>	Somewhat <u>agree</u>
I could feel the medication begin to work right away	Strongly <u>agree</u>	Strongly <u>agree</u>	Somewhat <u>agree</u>
I felt physical sensations shortly after taking the medication that reassured me that it was working	Strongly <u>disagree</u>	Strongly <u>agree</u>	Neither agree nor disagree
The medication worked as quickly as my rescue medication	Neither agree nor disagree	Strongly <u>agree</u>	Somewhat <u>disagree</u>
I was satisfied with how quickly I felt the medication begin to work	Strongly <u>agree</u>	Strongly <u>agree</u>	Somewhat <u>agree</u>
Monthly out-of-pocket cost of the medication	\$40	\$70	\$50
Which medication would you choose if these were your only options?	☐	☐	☐

Next

Figure 2. Patient choice between two hypothetical maintenance treatments and their current maintenance treatment.

was working" (Physical Sensations), with a mean relative importance weight of 0.7 ($p = 0.1433$), and "The medication worked as quickly as my rescue medication" (Rescue), with a mean relative importance weight of 2.8 ($p = 0.0007$). All five items were important to asthma patients to some degree; however, the mean relative importance of the Physical Sensations attribute was not statistically significantly different from zero ($p = 0.1433$; Fig. 3).

Predicted Preferences for Hypothetical Maintenance Treatments

We predicted the percentage of patients who preferred each treatment, for each of three pairs of hypothetical treatment profiles defined by OEQ outcomes¹: medication A versus medication B ("strongly agree" versus "strongly disagree" on Satisfied),² medication C versus medication D ("strongly agree" versus "strongly disagree" on Works Right Away), and³ medication E versus medication F ("strongly agree" versus "strongly disagree" on Satisfied and "strongly agree" versus "strongly disagree" on Works Right Away). The results indicate the following (Table 3):

- Medication A versus Medication B. When offered a choice, 80% ($p < 0.0001$) of patients preferred a maintenance medication with which they are "satisfied with how quickly they feel it begin to work."
- Medication C versus Medication D. When offered a choice, 62% ($p < 0.0001$) of patients preferred a maintenance medication that they feel "begins to work right away."

- Medication E versus Medication F. When offered a choice, 87% ($p < 0.0001$) of patients preferred a maintenance medication with which they are "satisfied with how quickly they feel it begin to work" and that they feel "begins to work right away."

Split-Sample Analyses

Among the split samples analyzed in this study, the mean relative importance of OEQ outcomes differ only between subsamples stratified by self-reported symptom severity. Specifically, we found that patients who rated their current symptoms as moderate, moderate-to-severe, and severe yielded statistically significantly different results than patients who rated their current symptoms as mild or mild-to-moderate (Fig. 4). The primary difference between these subgroups was the mean relative importance of Works Right Away ($p < 0.0001$ for moderate, moderate-to-severe, and severe groups, and $p = 0.0802$ for mild and mild-to-moderate groups). Patients who rated their asthma symptoms as moderate, moderate-to-severe, or severe found this outcome to be almost six times as important as did patients who rated their asthma symptoms as mild or mild-to-moderate ($p < 0.05$). Likewise, predicted preferences for different hypothetical treatments varied between these two groups (Table 3). Among patients with more severe symptoms, 70% ($p < 0.0001$) preferred a maintenance medication that they could feel begin to work right away compared with 55% ($p < 0.0001$) of patients with less severe symptoms.

Table 2 Demographic characteristics for full study sample

Characteristics	Number (%) of Patients (<i>n</i> = 509)
Gender	
Male	145 (28.5)
Female	364 (71.5)
Age (yr)—mean (SD)	55.4 (12.9)
Marital status	
Married	295 (57.9)
Single	72 (14.2)
Divorced	89 (17.5)
Widowed	45 (8.8)
Separated	8 (1.6)
Race	
White, non-Hispanic	437 (85.9)
Black, non-Hispanic	33 (6.5)
Hispanic	18 (3.5)
Other, non-Hispanic	4 (0.8)
Two or more races, non-Hispanic	17 (3.3)
Time since diagnosis (yr)	
<0.5	2 (0.4)
0.5–1	1 (0.2)
1–2	29 (5.7)
2–5	75 (14.7)
5–10	102 (20.1)
>10	299 (58.7)
Don't know	1 (0.2)
Self-reported severity of asthma symptoms	
Mild	82 (16.1)
Mild-to-moderate	134 (26.3)
Moderate	131 (25.7)
Moderate-to-severe	129 (25.4)
Severe	25 (4.9)
Don't know	7 (1.4)
Refused to answer	1 (0.2)
Taken combination maintenance medication within the past week?	
Yes	479 (94.1)
No	30 (5.9)

DISCUSSION

A number of studies have examined patient preferences for asthma symptom relief. For example, Osman and colleagues²⁹ found that relieving cough and breathlessness were the most important attributes of asthma treatments. In addition, Johansson and colleagues³⁰ and Bender and colleagues³¹ found that time to onset and immediate onset of action were important attributes of asthma treatments. In this study, we estimated patient preferences for onset of effect of combination ICS/LABA maintenance

medications as measured by the five onset-of-effect domains of the OEQ. Our findings show that patients with asthma have well-defined preferences for specific attributes of perceived onset of effect. The OEQ outcome most important to patients in this study was “I was satisfied with how quickly I felt the medication begin to work” (Satisfied). The least important OEQ outcomes was “I felt physical sensations shortly after taking the medication that reassured me it was working” (Physical Sensations), indicating that this OEQ outcome has very little influence on preferences for perceived onset of effect among patients with asthma.

Recent guidelines from the National Heart, Lung, and Blood Institute of the National Institutes of Health recommend that physicians determine a patient's treatment goals and preferences for treatment and involve patients in treatment decision making.³² These guidelines also recommend that physicians monitor patient satisfaction with both asthma control and quality of care to promote medication adherence. Studies indicate that single-inhaler combination maintenance treatments for asthma may improve treatment adherence and persistence compared with combination treatments that require multiple inhalers.^{33,34} In addition, Shapiro and colleagues³⁵ note that a simple combination of a long-acting bronchodilator and an ICS with quick onset of action could provide patients with significant clinical benefits and increase patient satisfaction and medication adherence.

The results of this study reinforce the importance of the results of the clinical trials that measured responses to items 2 (Works Right Away) and 5 (Satisfied) of the OEQ.¹² Specifically, these results show that perceived onset of effect, particularly patients' ability to feel the medication begin to work right away and patients' satisfaction with how quickly they feel the medication begin to work, are of significant value to patients with asthma. In addition, patients taking ICS/LABA combination medication whose symptoms were poorly controlled expressed a very strong preference for medications they could feel begin to work right away.

Although SC methods are widely used in health economics to elicit preferences, assess health-related quality of life, and evaluate marketing strategies, they have limitations. One inherent limitation is that patients evaluate hypothetical treatments. These constructed trade-off questions are intended to simulate possible clinical decisions but do not have the same clinical, financial, and emotional consequences of actual decisions. Thus, differences can arise between stated and actual choices. We have attempted to minimize such potential differences by offering alternatives that mimic real-world trade-offs as closely as possible. In addition, some health professionals are skeptical that people have sufficient understanding of

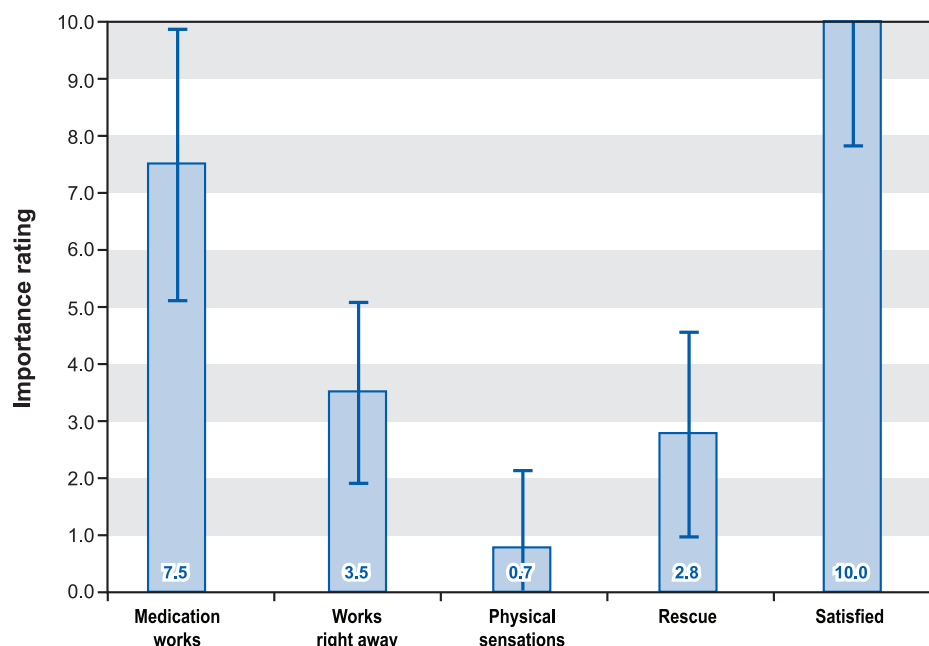


Figure 3. Mean relative importance of onset-of-effect questionnaire outcomes: full sample. Mean importance weight was estimated by taking the difference between the parameters for the highest and lowest levels. Importance ratings range from 0 to 10, where 0 represents the lowest level on the most important maintenance medication attribute level and 10 represents the highest level on the most important maintenance medication attribute level. Each of the remaining attributes is then assigned a relative importance rating between these extremes based on the difference in parameter estimates for the highest and lowest levels of the attribute. The vertical bars surrounding each mean importance weight denote the 95% confidence interval about the point estimate.

Table 3 Predicted preferences for three pairs of hypothetical medications

Medication	Medication Attributes					Percent Predicted Preference Share (95% Confidence Interval)		
	Medication Works	Works Right Away	Physical Sensations	Rescue	Satisfied	Full Sample	Mild Symptoms	Severe Symptoms
A	Strongly agree	Neither	Neither	Neither	Strongly agree	80 (75, 85)	83 (75, 89)	79 (70, 85)
B	Strongly agree	Neither	Neither	Neither	Strongly disagree	20 (15, 25)	17 (11, 25)	21 (15, 30)
C	Strongly agree	Strongly agree	Neither	Neither	Strongly agree	62 (57, 67)	55 (48, 63)	70 (63, 77)
D	Strongly agree	Strongly disagree	Neither	Neither	Strongly agree	38 (33, 43)	45 (37, 52)	30 (23, 37)
E	Strongly agree	Strongly agree	Neither	Neither	Strongly agree	87 (81, 91)	86 (77, 92)	90 (81, 94)
F	Strongly agree	Strongly disagree	Neither	Neither	Strongly disagree	13 (9, 19)	14 (8, 23)	10 (6, 18)

treatment information to competently evaluate treatment alternatives. The survey instrument, which is based on a validated patient instrument, provided balanced information on treatment attributes, but some patients might have had difficulty assimilating and applying the information provided. Diagnosis and symptom severity among patients in this study was

self-reported and not confirmed by physician consultation or chart review. However, we believe the likelihood is small that people without asthma would be likely to complete a study such as this because the study is cognitively challenging and requires an investment in time in exchange for little personal gain. Finally, we recruited patients through an Internet-based

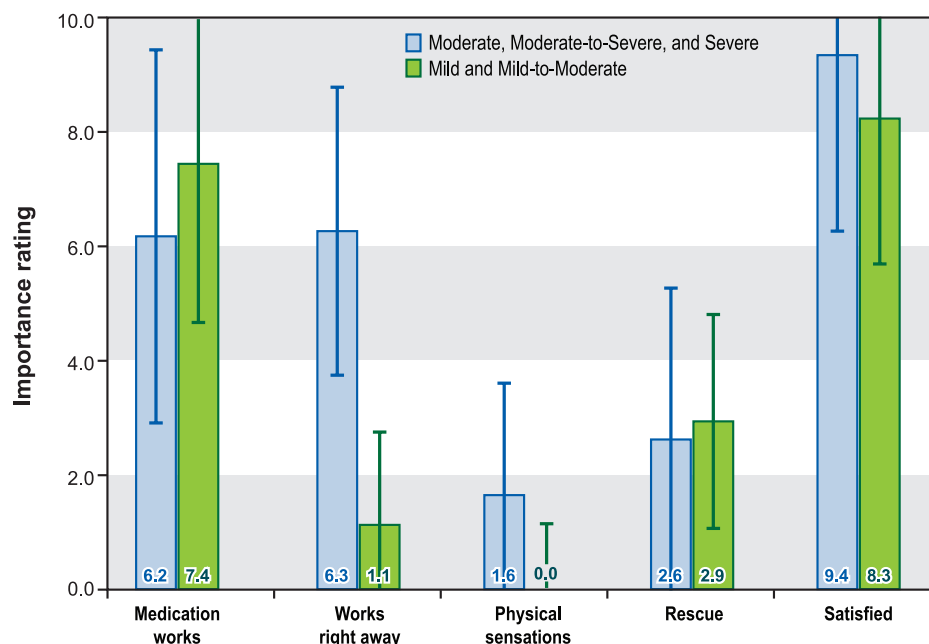


Figure 4. Mean relative importance of onset-of-effect questionnaire outcomes: sample split by self-reported severity of asthma symptoms. Mean importance weight was estimated by taking the difference between the parameters for the highest and lowest levels. Importance ratings range from 0 to 10, where 0 represents the lowest level on the most important maintenance medication attribute level and 10 represents the highest level on the most important maintenance medication attribute level based on the full-sample results. Each of the remaining attributes is then assigned a relative importance rating between these extremes based on the difference in parameter estimates for the highest and lowest levels of the attribute. The vertical bars surrounding each mean importance weight denote the 95% confidence interval about the point estimate.

panel that is representative of the entire U.S. population; however, that does not mean that the sample used in this study necessarily was representative of asthma patients in the U.S. population who use combination ICS/LABA maintenance treatments. For example, there was a higher percentage of women in our sample (71.5%) compared with 65% in the population of people with asthma.³⁶ Thus, we can not say that these results are representative of the entire population of asthma patients in the United States using combination ICS/LABA.

In conclusion, we found that patients with asthma have clear preferences for perceived onset of effect in maintenance medications. Given the high prevalence of asthma and its adverse effects on quality of life and significant lost productivity, maintenance medications that improve on onset of effect, especially a patients' ability to feel the medication work right away and patient satisfaction with how quickly the medication works, may increase the use of and adherence to maintenance medications among this population and reduce the burden of asthma in the United States.

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