

Treatment of moderate to severe asthma: patient perspectives on combination inhaler therapy and implications for adherence

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Abstract: Symptom control in patients with moderate to severe persistent asthma is essential to reduce the significant morbidity associated with the disease. Poor adherence to controller medications has been identified as a major contributing factor to the high level of uncontrolled asthma. This review examines patient perspectives on, and preferences for, controller medications (inhaled corticosteroid and long-acting β_2 -agonist combinations [ICS/LABA]), and how this may affect adherence to therapy. Fluticasone/salmeterol and budesonide/formoterol, the currently available ICS/LABA combination products, have similar efficacy and tolerability based on a recent meta-analysis of asthma trials. Adherence is higher with the combination ICS/LABAs than when the components are administered separately. Investigations into patient preferences for desirable attributes of asthma medications indicate that an effective reliever with a fast onset and long duration of action is preferred and may lead to improved adherence. This rapid onset of effect was perceived and highly valued in patient surveys, and was associated with greater patient satisfaction. Thus, future research should be directed at therapy that offers both anti-inflammatory activity and a rapid onset of bronchodilator effect. To further improve patient adherence and treatment outcome, the effect of these characteristics as well as other factors on adherence should also be investigated.

Keywords: budesonide/formoterol, fluticasone/salmeterol, adherence, onset of effect, patient satisfaction

Clinician and patient perspectives on asthma control

The overarching goal of asthma management is to achieve and maintain asthma control. Moderate to severe persistent asthma is associated with substantial morbidity if not adequately controlled.¹ Despite the availability of evidence-based strategies for maximizing asthma control, the results of a national Web-based survey of 1812 adults with persistent asthma indicated that 55% had inadequate control of their asthma (Figure 1).² While this shortcoming may be due in part to the limitations of current therapy, the results of the Gaining Optimal Asthma Control (GOAL) study³ have shown that most patients can achieve and maintain guideline-defined control. Using a dose escalation strategy, patients with a wide range of asthma severity achieved control; at 1 year, 41% of patients had totally controlled asthma with inhaled corticosteroid (ICS)/long-acting β_2 -agonist (LABA) combination therapy versus 28% with ICS alone, while 71% maintained at least well-controlled asthma with ICS/LABA versus 59% with ICS alone.³ In addition, patients who achieved totally or well-controlled asthma for 8 weeks maintained a high level of asthma stability, whereas patients whose asthma

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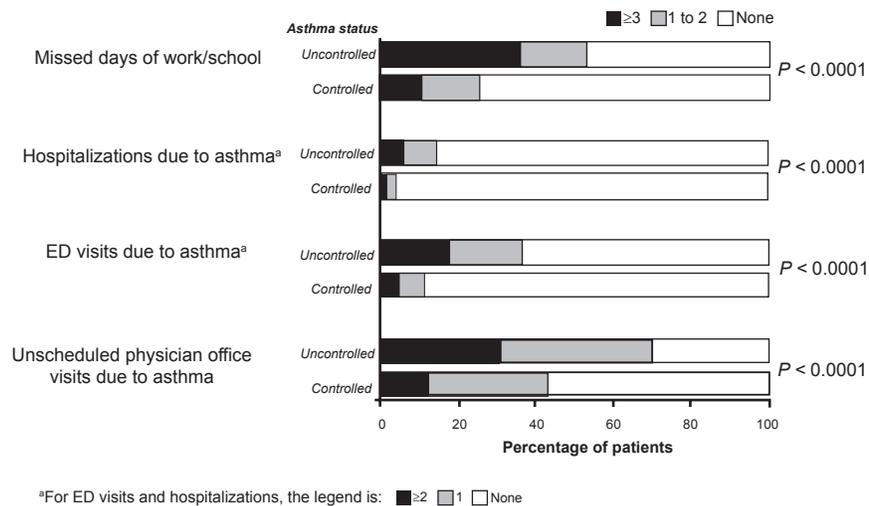


Figure 1 Healthcare use and missed work/school in the past year in 809 patients with controlled asthma and 1003 patients with uncontrolled asthma. Drawn from data of Peters et al.²
Abbreviation: ED, emergency department.

was not well controlled had less stable levels of control and were more likely to make unscheduled use of healthcare resources.⁴ As the goal of treatment was to achieve total asthma control, most patients were receiving the maximum permitted dose of ICS or ICS/LABA by the end of the study. Although the study was not designed to establish a clinical model for the treatment of asthma, the results indicated that optimal control was most likely to occur with ICS/LABA combination therapy.

Although it is recognized that asthma control cannot be obtained in all patients,³ poor adherence to prescribed controller medications is a significant contributor to the high level of uncontrolled asthma.⁵⁻⁷ Findings from a retrospective analysis of a large healthcare database showed that almost half of the patients with asthma failed to renew their prescription for controller medication in the first year of treatment.⁸ The results of another retrospective study of 405 patients with asthma in a Michigan-based health maintenance organization revealed that adherence to ICS therapy during the 2-year observation period was only 50%, and lack of adherence to ICS therapy was responsible for 60% of all asthma-related hospitalizations.⁷

Another reason for suboptimal asthma control may be healthcare providers' failure to implement asthma treatment guidelines. Despite concerted efforts over the past decade to raise awareness of the NHLBI guidelines among primary care physicians, several urban-based studies have reported poor provider adherence to key asthma treatment recommendations, both in the pediatric-adolescent^{9,10} and adult^{11,12} outpatient settings. A recent (2003 to 2007) survey of 202 adult primary healthcare providers in inner-city

New York assessed their adherence to 5 NHLBI guideline components.¹² The survey results revealed suboptimal levels of implementation of peak flow monitoring, action plans, and referral for allergy testing, as reflected by adherence rates of 34%, 9%, and 10%, respectively.¹² These shortcomings were attributed to the physicians' lack of confidence in their ability to effectively implement the guideline recommendations and their low expectations of treatment outcome.¹²

Medication adherence is a complex issue, influenced by factors related to patients, healthcare providers, disease severity, and therapy. Improving adherence requires an approach that addresses these multiple factors.^{5,13} Findings from several studies have shown the need for patient education about the importance of daily use of controller medication even when symptoms are absent or not bothersome.¹⁴⁻¹⁹ Patients who have a "no symptoms, no asthma" belief have been shown to be significantly less likely to use ICS when they are asymptomatic and are less likely to engage in other self-management behaviors.²⁰

Conversely, certain patient beliefs and perspectives may promote adherence to controller medication. For example, adherence is higher in those who believe that their controller medication is effective.¹⁸ Likewise, patients prefer treatments with immediate and noticeable effects, since this provides assurance that their medication is working.¹⁴ The purpose of this review is to examine how patient perspectives on, and preferences for, controller medication affect treatment adherence. The review focuses on the ICS/LABA combination products recommended by the NHLBI and GINA guidelines for the treatment of moderate to severe persistent asthma.^{21,22}

Combination ICS/LABA controller medications

LABA is recommended in combination with ICS for long-term control and prevention of symptoms in patients aged 5 years or older who have moderate or severe persistent asthma or asthma that is inadequately controlled by ICS alone. ICS and LABA can be administered via separate inhalers (concurrent therapy) or via a single inhaler containing both drugs. Two single-inhaler ICS/LABA therapies are currently available and have been demonstrated to be effective and well tolerated: budesonide in combination with formoterol,^{23–26} and fluticasone in combination with salmeterol.^{27–31} Fluticasone/salmeterol (100/50 µg) is indicated for use in children aged 4 to 11 years, as well as in adolescents and adults.³² Currently, budesonide/formoterol pressurized metered-dose inhaler (pMDI) is indicated for use in individuals aged 12 years or older in the United States.³³ Outside the United States, budesonide/formoterol dry powder inhaler (DPI) 80/4.5 µg and 160/4.5 µg doses are approved for patients aged 4 years or older, and the 320/9 µg dose is indicated for patients aged 12 years or older.

There are several potential advantages to single-inhaler combination therapy. Preclinical research has suggested that a potential synergy between corticosteroids and β_2 -agonists at the cellular and molecular level may translate into clinical benefits if they are deposited in the lungs simultaneously.³⁴ Furthermore, ICS nonadherence is less likely with the combination product in a single inhaler, because it removes any confusion or inconvenience associated with the use of 2 separate inhalers.

Comparative safety and efficacy of fixed-dose regimens: budesonide/formoterol versus fluticasone/salmeterol combination therapy

The safety and efficacy of fixed doses of budesonide/formoterol and fluticasone/salmeterol have been directly compared in several large, randomized, controlled trials,^{35–39} which formed the basis of a recently published Cochrane meta-analysis.⁴⁰ Drawing on 5 randomized studies including data from 5537 adolescent and adult patients with asthma (Table 1), the meta-analysis found that budesonide/formoterol and fluticasone/salmeterol were equally effective and well tolerated, with no significant differences between treatments on primary efficacy outcomes (exacerbations requiring oral steroids or hospitalization; serious adverse events [including asthma-related deaths and intubation]) (Table 2) or secondary

efficacy outcomes (exacerbations leading to emergency department visit/hospital admission, morning and evening peak flow, clinical spirometry measures, symptoms, reliever medication use, and tolerability).⁴⁰

Onset of bronchodilator action of fixed-dose regimens: budesonide/formoterol versus fluticasone/salmeterol combination therapy

One characteristic that differs between budesonide/formoterol and fluticasone/salmeterol with the potential to influence patient preference is the onset of effect. Comparative trials have shown that formoterol has a rapid onset of effect, similar to that of albuterol, and significantly more rapid than that of salmeterol.^{41,42} Similar results have been found in randomized, crossover studies with the combination inhalers budesonide/formoterol and fluticasone/salmeterol. When both combinations were delivered by DPI, budesonide/formoterol (160/4.5 µg and 320/9 µg) showed a significantly faster onset of bronchodilatory action than fluticasone/salmeterol (250/50 µg), as measured by mean forced expiratory volume in 1 second (FEV_1) at 3 minutes after inhalation.^{43,44} Likewise, a comparison of the bronchodilatory effects of budesonide/formoterol pMDI (160/9 µg), fluticasone/salmeterol DPI (250/50 µg), and albuterol pMDI (180 µg) showed that the improvement in FEV_1 observed at 3 minutes after dosing was significantly greater with budesonide/formoterol pMDI than with fluticasone/salmeterol DPI, and similar to that with albuterol pMDI.⁴⁵

ICS/LABA combination therapy: patient adherence, satisfaction, and preferences

Adherence to ICS/LABA combination therapy

Use of combination ICS/LABA therapy may help with patient nonadherence. Administration of the ICS/LABA combination in a single inhaler simplifies the treatment regimen and improves patient adherence, as shown by analyses of medical and pharmacy claims from a large managed care organization and Medicaid patients.^{46,47} In both analyses, patient adherence was significantly greater with fluticasone/salmeterol administered in a single inhaler than with the individual drug components administered separately. In 1 analysis, short-acting β_2 -agonist (SABA) use was significantly lower when combination fluticasone/salmeterol therapy was administered in a single inhaler than

Table 1 Randomized, controlled studies of fixed-dose budesonide/formoterol versus fluticasone/salmeterol combination therapy in asthma

Study	Design	Patients	Treatments (FD arms)	Primary efficacy outcome	Safety outcomes
Aalbers et al ³⁶	4-week, randomized, double-blind, parallel-group 6-month, open-label, extension phase	Symptomatic patients aged ≥ 12 years with asthma ≥ 6 months Mean symptom score 1.5 Mean ICS 735 $\mu\text{g}/\text{day}$ Mean FEV ₁ 84% predicted	BUD/FM 160/4.5 $\mu\text{g} \times 2$ inhalations bid (n = 215) FP/SM: 250/50 $\mu\text{g} \times 1$ inhalation bid (n = 224)	Similar: odds of achieving a well-controlled asthma week for FP/SM and BUD/FM (OR: 1.29; 95% CI: 0.98, 1.69)	Similar AE incidence Most mild to moderate in severity
Dahl et al ³⁸	24-week, randomized, double-blind, parallel group	Patients ≥ 18 years with asthma ≥ 6 months Mean FEV ₁ 79% predicted Previous ICS use (BDP 1000–2000 $\mu\text{g}/\text{day}$ or equivalent)	BUD/FM 200/6 $\mu\text{g} \times 2$ inhalations bid (n = 697) FP/SM: 250/50 $\mu\text{g} \times 1$ inhalation bid (n = 694)	Similar rates of exacerbations: FP/SM, 2.69; BUD/FM, 2.79 (OR: 0.96; 95% CI: 0.84, 1.10)	Similar AE incidence Both drugs similarly well tolerated
Kuna et al ³⁹	6-month, randomized, double-blind, parallel-group	Symptomatic patients ≥ 12 years with asthma ≥ 6 months Mean FEV ₁ 73% predicted Mean ICS 744–750 $\mu\text{g}/\text{day}$	BUD/FM 320/9 $\mu\text{g} \times 1$ inhalation bid (n = 1105) FP/SM: 125/25 $\mu\text{g} \times 2$ inhalations bid (n = 1123)	Similar rates of severe exacerbations for BUD/FM vs FP/SM (HR: 0.91; 95% CI: 0.72, 1.16)	Similar AE incidence and severity Both drugs well tolerated
Busse et al ³⁷	7-month, randomized, open-label	Patients ≥ 12 years with moderate to severe persistent asthma ≥ 6 months Mean FEV ₁ ~78% predicted Mean ICS ~550 $\mu\text{g}/\text{day}$	BUD/FM 160/4.5 $\mu\text{g} \times 2$ inhalations bid (n = 427) FP/SM: 250/50 $\mu\text{g} \times 1$ inhalation bid (n = 406)	Similar times to first asthma exacerbation for BUD/FM vs FP/SM (HR: 0.99; 95% CI: 0.79, 1.25)	Similar AE pattern; mostly mild or moderate severity Both drugs well tolerated
SAM40048 ³⁵	12-week, randomized, double-blind, parallel group	Symptomatic patients > 18 years with moderate asthma Mean symptom score ≥ 1 Mean FEV ₁ 65% predicted Previous ICS use (BDP 1000 $\mu\text{g}/\text{day}$ or equivalent)	BUD/FM 200/6 $\mu\text{g} \times 1$ inhalation bid (n = 127) FP/SM: 250/50 $\mu\text{g} \times 1$ inhalation bid (n = 121)	Similar: changes in FEV ₁ % predicted after 12 weeks, mean (SD): BUD/FM, 10.9 (13.3); FP/SM, 14.0 (16.4)	Similar AE incidence

Abbreviations: AE, adverse event; BDP, beclomethasone dipropionate; BUD, budesonide; CI, confidence interval; FD, fixed dose; FEV₁, forced expiratory volume in 1 second; FM, formoterol; FP, fluticasone propionate; HR, hazard ratio; ICS, inhaled corticosteroid; OR, odds ratio; SD, standard deviation; SM, salmeterol.

Table 2 Primary outcomes of a meta-analysis comparing the efficacy and safety of fluticasone/salmeterol versus budesonide/formoterol combination therapy⁴⁰

Outcome	Study	Fluticasone/ salmeterol n/N (%)	Budesonide/ formoterol n/N (%)	Odds ratio (95% CI)
Exacerbations requiring oral steroid treatment	Busse et al ³⁷	37/404 (9.2)	37/422 (9.2)	1.05 (0.65, 1.69)
	Kuna et al ³⁹	109/1199 (9.1)	108/1099 (9.8)	0.92 (0.69, 1.21)
	Dahl et al ³⁸	63/694 (9.1)	79/697 (11.3)	0.78 (0.55, 1.11)
	Total	209/2297 (9.1)	224/2218 (10.1)	0.89 (0.73, 1.09)
Exacerbations requiring hospitalization	Aalbers et al ³⁶	0/219 (0.0)	1/215 (0.5)	0.33 (0.01, 8.04)
	Busse et al ³⁷	2/404 (0.5)	1/422 (0.2)	2.09 (0.19, 23.19)
	Kuna et al ³⁹	15/1123 (1.2)	13/1105 (1.2)	1.14 (0.54, 2.40)
	Dahl et al ³⁸	4/694 (0.6)	1/697 (0.1)	4.03 (0.45, 36.19)
Total	21/2440 (0.8)	16/2439 (0.7)	1.29 (0.68, 2.47)	
Asthma-related serious AEs	Aalbers et al ³⁶	0/224 (0.0)	1/215 (0.5)	0.32 (0.01, 7.86)
	Kuna et al ³⁹	15/1119 (1.3)	12/1099 (1.1)	1.23 (0.57, 2.64)
	Dahl et al ³⁸	6/697 (0.9)	1/700 (0.1)	6.07 (0.73, 50.55)
	Total	21/2040 (1.0)	14/2014 (0.7)	1.47 (0.75, 2.86)

Notes: Odds ratio represents the event risk for fluticasone/salmeterol relative to budesonide/formoterol.

Abbreviations: AEs, adverse events; CI, confidence interval.

when administered separately;⁴⁷ however, this finding was not seen in a study by Stempel and colleagues.⁴⁶ Retrospective analysis of matched cohort data from a Canadian provincial healthcare and public drug insurance plan database revealed that combination ICS/LABA therapy was associated with significantly greater persistence, better treatment adherence, fewer asthma exacerbations, and lower use of SABAs than concurrent inhaler therapy.⁸ These studies are retrospective and based on pharmacy claims data and not direct measures of adherence.

Patient satisfaction with ICS/LABA combination therapy

Satisfaction with treatment is an important factor in a patient's resolve to continue daily asthma medication. A search of the medical literature on patient preference or satisfaction with ICS/LABA therapy was conducted using PubMed, EMBASE, and ISI Web of Knowledge (Thomson Reuters), as well as a search of clinicaltrials.gov for ongoing trials, revealing overall limited information. Patient satisfaction with ICS/LABA combination therapy administered from a single inhaler was investigated in 2 randomized, double-blind, placebo-controlled, 12-week studies of budesonide/formoterol pMDI.^{48,49} In the first study, conducted in 405 patients with mild to moderate persistent asthma, budesonide/formoterol pMDI 160/9 µg bid was compared with budesonide pMDI 160 µg bid and formoterol DPI 9 µg bid.⁴⁹ Patient satisfaction was assessed using the Patient Satisfaction with Asthma

Medication (PSAM) questionnaire,⁵⁰ a validated, 23-item, asthma-specific instrument covering 4 domains: perception of medication index, control relief index, comparison with other medications index, and inhaler index (this last domain was not assessed, because all patients used both types of inhalers [pMDI and DPI]). The perception of medication index assesses satisfaction with medical benefits received, overall perception, influence on sense of well being, and whether a patient would recommend the treatment to others. The control relief index rates the onset, degree, and duration of symptom relief, and the patient's willingness to continue treatment. The comparison with other medications index compares the current treatment versus all other inhaled medications for onset, degree, and duration of relief. Scores range from 0 to 100, with 0 representing the lowest level of satisfaction and 100 representing the highest.⁵⁰

After 12 weeks of treatment, mean PSAM scores were significantly higher with budesonide/formoterol pMDI than with budesonide pMDI or formoterol DPI on all 3 assessed indices (Figure 2).⁴⁹ A greater proportion of patients also reported higher satisfaction with budesonide/formoterol pMDI than with the other treatments on the individual items within each of the 3 assessed PSAM indices. These results suggest not only that treatment with budesonide/formoterol pMDI leads to greater satisfaction with asthma medication, but also that both components contribute to this improvement.⁴⁹

In the second study, patient-reported outcomes were compared in 553 adults with moderate to severe persistent

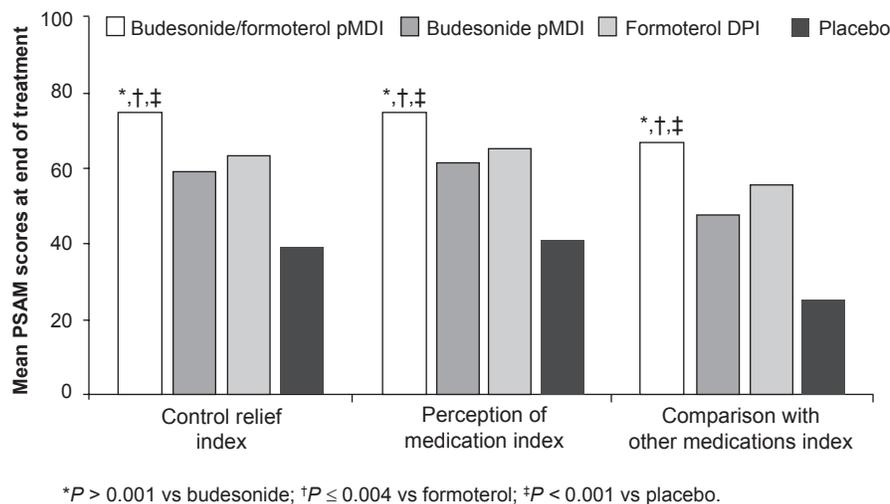


Figure 2 Mean Patient Satisfaction with Asthma Medication (PSAM) index scores at the end of 12 weeks of treatment with budesonide/formoterol, budesonide alone, formoterol alone, or placebo. Drawn from data of Murphy et al.⁴⁹

Abbreviations: DPI, dry powder inhaler; pMDI, pressurized metered-dose inhaler.

asthma who were randomized to treatment with budesonide/formoterol pMDI 320/9 μg bid (administered via a single inhaler), budesonide pMDI 320 μg bid plus formoterol DPI 9 μg bid (administered consecutively via 2 separate inhalers), budesonide pMDI 320 μg bid, formoterol DPI 9 μg bid, or placebo.⁴⁸ Patient health-related quality of life was assessed using the standardized Asthma Quality of Life Questionnaire (AQLQ[S]),⁵¹ the Medical Outcomes Survey (MOS) Sleep Scale,⁵² and the PSAM questionnaire. No significant differences in patient-related outcomes were noted between budesonide/formoterol and budesonide plus formoterol (ie, between combination therapy administered from a single inhaler versus 2 separate inhalers); however, end-of-treatment improvements in AQLQ(S) overall and domain scores and in PSAM scores for control relief and perception of medication were significantly greater with budesonide/formoterol pMDI than with the individual components.

Patient preferences for attributes of asthma therapy

Conjoint analysis is a technique used in market research to investigate the relative importance of groups of attributes of consumer products, and it can also be used to analyze patient preferences for various treatment options.⁵³ It provides a method for comparing the value to the patient of desirable attributes (eg, efficacy) versus undesirable ones (eg, high cost) and for identifying which factors influence patient preference for one regimen over another. Patient preference for attributes of asthma medication was investigated using conjoint analysis in a Swedish study involving 298 adult

patients with asthma receiving ICS plus SABA, ICS plus LABA, or ICS/LABA.⁵⁴ Different combinations of 6 attributes of asthma treatment were rated by questionnaire with predefined levels for each attribute. These included: (1) type of maintenance treatment (ICS alone, LABA + ICS, or ICS/LABA in a single inhaler); (2) need for additional inhaler for acute symptom relief (yes/no); (3) time to onset of action of reliever (≤ 3 minutes, 10 to 15 minutes); (4) duration of action of reliever (3 to 6 hours, ≥ 12 hours); (5) number of symptom-free days per month (<10, 10 to 14, 15 to 20, >20); and (6) out-of-pocket costs per month (\$k100, 240, 380, 520). Conjoint analysis showed that patients focused primarily on the effectiveness of treatment. While the most important aspect of asthma maintenance treatment was the number of symptom-free days, this was found only when the number of symptom-free days increased from <10 to >20 per month. The highest-ranked preferences were treatment with a reliever with fast onset and long duration of action (preferred by 78% of patients) and treatment with an ICS/LABA combination inhaler rather than separate inhalers (preferred by 50% of patients). The preferred asthma regimen was an ICS/LABA combination that could be used for both controller and reliever therapy. Overall, 85% of patients preferred an alternative treatment to their current regimen and were willing to pay more (on average about US\$36) for the alternative.⁵⁴

More recently, a US nationwide telephone survey of 200 randomly selected adults with asthma was conducted to establish the factors that influence patients' adherence to asthma controller medication.⁵⁵ When questioned about treatment-related factors that might improve their adherence,

the most frequent responses were: (1) “If it controlled my symptoms better”; (2) “If it had long-lasting control of my symptoms”; (3) “If it meant I would need rescue medication less often”; (4) “If it meant I would need less additional medication to control my asthma overall”; (5) “If I knew I would feel better and could be more active without having asthma symptoms”; and (6) “If I could feel it helping my asthma soon after taking it.” Nonadherence was primarily the consequence of an active decision to use medication only as needed. A subgroup of patients who reported poor adherence to their controller medication ($n = 75$) listed different factors that might improve their adherence: (1) “If I could do more things I normally can’t do now”; (2) “If I could feel it helping my asthma soon after taking it”; (3) “If it had long-lasting control of my symptoms”; (4) “If it controlled my symptoms better”; (5) If it meant I would need rescue medication less often”; and (6) “If I could be certain that it was safe.” Many of the 200 patients strongly preferred a medication that worked quickly; this preference was especially apparent in the nonadherent group.⁵⁵

Patient preference for a rapid bronchodilator effect has been investigated recently using a newly developed measure, the Onset of Effect Questionnaire (OEQ).⁵⁶ The OEQ is a validated weekly diary that elicits ratings for 5 items: during the past week (1) you could tell that your study medication was working; (2) you could feel your study medication begin to work right away; (3) you felt physical sensations shortly after taking your medication that reassured you that it was working; (4) your study medication worked as quickly as your albuterol; and (5) you were satisfied with how quickly you felt your study medication begin to work.⁵⁶ Perception of, and

satisfaction with, the feeling that controller therapy is working right away as measured by the OEQ items 2 and 5 has been shown to be a significant predictor of overall satisfaction with medication and satisfaction with the onset and duration of relief of asthma symptoms, as assessed by the PSAM (Figure 3).⁵⁶ This suggests that patients who perceive that their medication is acting rapidly will not only receive positive reinforcement from use of the medication, but will also be more satisfied with treatment, possibly resulting in better treatment adherence.⁵⁶ In 2 double-blind, randomized, placebo-controlled clinical trials employing the OEQ in asthma, significantly more budesonide/formoterol-treated patients than budesonide- or placebo-treated patients reported that they could feel their study medication beginning to work right away.⁵⁷

Clinicians’ perspectives regarding the value to the patient of a perceived rapid onset of treatment effect have also been evaluated.⁵⁸ A 12-member consensus panel of community-based healthcare professionals who reviewed the above-mentioned OEQ findings with budesonide/formoterol pMDI, but were blinded to the drug name,⁵⁶ unanimously concluded that the fact that patients could feel their medication working right away was clinically relevant and meaningful to decision making, and that this attribute might improve patient adherence.⁵⁸

Patient satisfaction with ICS/LABA: budesonide/formoterol versus fluticasone/salmeterol

Patient satisfaction with the budesonide/formoterol pMDI (adjustable-dose and fixed-dose) compared with the fluticasone/salmeterol DPI has been assessed using the Asthma Treatment

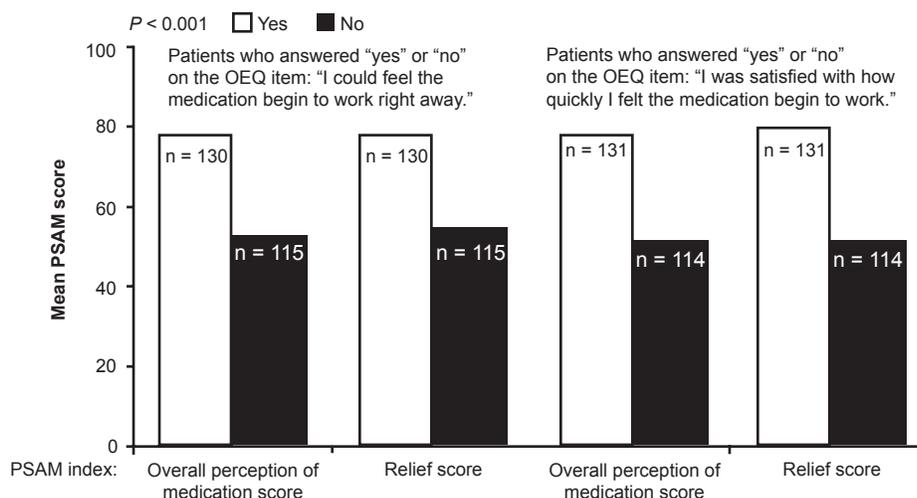


Figure 3 Relationship between perception of, and satisfaction with, the feeling that medication is working right away on the Onset of Effect Questionnaire (OEQ) and ratings from the Patient Satisfaction with Asthma Medication (PSAM) index on satisfaction with medication and asthma symptom relief scores. Drawn from data of Murphy et al.⁴⁹

Satisfaction Measure (ATSM)⁵⁹ in a large, randomized, open-label, multicenter, 7-month study of adult patients with moderate to severe persistent asthma.⁶⁰ The ATSM is a newly developed, validated instrument that incorporates the domains of patient expectations, treatment preferences, self-reported treatment outcomes, and overall treatment satisfaction.⁵⁹ As measured by the ATSM, patient satisfaction with treatment was greater with budesonide/formoterol (adjustable dose or fixed dose) than with fixed-dose fluticasone/salmeterol. Patients receiving adjustable-dose budesonide/formoterol reported significantly greater satisfaction on the ATSM overall score and scores for *feel medication working*, *dosing management*, and *timely relief of symptoms* compared with those receiving fixed-dose fluticasone/salmeterol. Patients receiving fixed-dose budesonide/formoterol reported significantly greater satisfaction for *timely relief of symptoms* and *feel medication working* scores than those receiving fixed-dose fluticasone/salmeterol.⁶⁰

In summary, assessment of patient satisfaction and preference for treatment provides insight into those features of combination controller medication that are important to patients and may lead to greater treatment adherence. These assessments showed that the rapid onset of bronchodilator effect associated with budesonide/formoterol was highly valued by patients and was associated with greater patient satisfaction than was fluticasone/salmeterol. However, it is important to note that patients' stated preference for rapid onset of effect does not necessarily mean improved adherence to therapy will be a direct result. Further studies are needed to evaluate the impact of this characteristic of an ICS/LABA combination on adherence.

Implications for future clinical research and development

Use of combination therapy for both controller and reliever therapy

Research suggests that patients would prefer an ICS/LABA combination that could be used as both controller and reliever medication.⁵⁴ The strategy of using a single ICS/LABA for both controller and reliever therapy, known by the acronym SMART (Symbicort® [budesonide/formoterol] Maintenance and Reliever Therapy), is currently approved outside the United States. Symbicort SMART is based on the premise that for patients who are already receiving a daily maintenance dose of budesonide/formoterol, use of as-needed budesonide/formoterol would allow more rapid adjustment of anti-inflammatory therapy in conjunction with

rapid relief of symptoms. More rapid ICS adjustment, in turn, is associated with improved asthma control. At the same time, the LABA component would provide rapid symptom relief. This premise has been confirmed by findings from numerous studies;^{39,61–65} however, further research is needed to determine if it leads to improved adherence to therapy.

The rapid onset of effect of formoterol is advantageous not only because it allows the combination with budesonide to be used as both controller and reliever therapy, but also because it contributes to patient satisfaction with treatment.⁵⁶ Pharmaceutical research and development should be directed toward combination therapies with rapid-acting LABAs, because of the importance to patients of rapid onset of action.^{54,56} Promising new ICS/rapid-acting LABA combinations include ciclesonide/formoterol, mometasone/formoterol, fluticasone/formoterol, and mometasone/indacaterol. Investigation into patient preference and the impact on adherence with these medications will be essential as we continue to advance asthma care.

Conclusions

Advances in the management of asthma are aimed at providing therapies that are not only safe and effective, but also have the potential for overcoming insufficient medication adherence, which is a critical barrier to successful treatment. Treatment with ICS/LABA is highly effective and recommended for patients whose asthma is not controlled on ICS alone. Combination treatment with a single inhaler is preferred by patients and is associated with improved adherence compared with ICS alone or ICS and LABA in separate inhalers.

In addition to the convenience of a single inhaler, patients prefer medications with a rapid onset of effect. Patients who exhibit poor adherence believed that a rapid onset of effect would improve their adherence to treatment. Currently available data based on patients' perspectives on ICS/LABA therapy suggests that patients receiving rapidly acting combination therapy perceive immediate benefit from their medication and experience high levels of satisfaction with treatment. Research is needed to evaluate if patient preference for a drug with rapid onset of effect results in improved adherence to therapy and outcome. Thus, future research should be directed at combination therapy that offers not only anti-inflammatory activity, but a rapid onset of bronchodilator effect.

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