

A Practical Guide to Implementing SMART in Asthma Management



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The use of a single inhaler containing the combination of an inhaled corticosteroid (ICS) and formoterol, a specific long-acting bronchodilator, for both maintenance and quick relief therapy (single maintenance and reliever therapy [SMART or MART]) is recommended by both the Global Initiative for Asthma and the National Asthma Education and Prevention Program Coordinating Committee in steps 3 and 4 of asthma management. This article provides practical advice about implementing SMART in clinical practice based on evidence and clinical experience. Fundamental to SMART is that ICS-formoterol provides quick relief of asthma symptoms similar to that of short-acting β_2 -agonists such as albuterol, while reducing the risk for severe asthma exacerbations and at an overall lower

ICS exposure. Most SMART clinical trials were in adults and adolescents (aged ≥ 12 years), using budesonide-formoterol 160/4.5 μg (delivered dose), one inhalation once or twice daily (step 3) and two inhalations twice daily (step 4). For both steps 3 and 4, patients take additional inhalations of budesonide-formoterol 160/4.5 μg , one inhalation whenever needed for symptom relief, up to a maximum for adults and adolescents of 12 total inhalations in any single day (delivering 54 μg formoterol). The efficacy and safety of SMART with budesonide-formoterol and beclomethasone-formoterol have been confirmed, but other ICS–long-acting bronchodilator combinations have not been studied. The SMART regimen should be introduced with a careful explanation of its role in self-management, preferably with a customized written asthma action plan. The cost to patients and the availability of SMART treatment will depend on the prescribed dose and national or local payer agreements. © 2021 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2022;10:S31-S8)

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INTRODUCTION

In 2020, the National Asthma Education and Prevention Program (NAEPP) published Focused Updates to Asthma Management Guidelines for US clinicians (2020 NAEPP Asthma Update)¹ that preferentially recommended the use of a combination inhaled corticosteroid (ICS)-formoterol inhaler for both maintenance and quick symptom relief (single maintenance and reliever therapy [SMART; also called MART]) at steps 3 and 4 in children aged 4 years or older and in adults. The 2020 NAEPP Asthma Update used the Grading of Recommendations, Assessment, Development and Evaluation framework to evaluate evidence regarding SMART and formulate recommendations about its use, and concluded that there was a high certainty of evidence regarding the benefit of this treatment approach in treatment steps 3 and 4 compared with same-dose ICS–long-acting β_2 -agonist (LABA) or higher-dose ICS therapy, plus short-acting β_2 -agonist (SABA) as needed, for individuals with asthma aged 12 years or more, and moderate-certainty evidence for children aged 4 to 11 years. For people aged 12 years or older with asthma, NAEPP gave a conditional recommendation with a high certainty of evidence for SMART compared with higher-dose ICS-LABA plus as-needed SABA. For people whose asthma is uncontrolled with daily ICS-LABA treatment plus as-needed SABA, the clinical trial evidence supports switching to SMART at the same or lower maintenance ICS-LABA dose

before considering a step-up of maintenance treatment.²⁻⁴ Single maintenance and reliever therapy is also preferentially recommended in steps 3 and 4 in the Global Initiative for Asthma (GINA) strategy report, the most recent update of which was published in 2021.⁵

The SMART regimen with budesonide-formoterol is approved for adults and adolescents (aged ≥ 12 years) by regulators in more than 120 countries and for children aged 4 to 11 years in a small number of countries (personal communication, AstraZeneca); budesonide-formoterol is manufactured by several other companies; and SMART with beclometasone-formoterol is approved by regulators in more than 70 countries for adults (aged ≥ 18 years) (personal communication, Chiesi). For US clinicians, although the combination of budesonide-formoterol is approved for daily use by the US Food and Drug Administration (FDA) for individuals aged 4 years and older (marketed as Symbicort), SMART regimens are not FDA-approved for any age group.

For US clinicians, although the change in the 2020 NAEPP Asthma Update is based on a moderate (for children aged 4-11 years) or high certainty of evidence (for adults and adolescents aged ≥ 12 years) for steps 3 and 4, its implementation presents several challenges.⁶ Global experience with SMART provides a resource that may prove useful for those who are new to the approach. This review addresses these issues and provides practical points for implementing SMART, based on evidence where available, and on clinical experience with this regimen.

This article was prepared by authors who also participated in developing reports by GINA (H.K. Reddel, E.D. Bateman, and J.A. Krishnan) and NAEPP (M.C. Cloutier, M. Schatz, and J.A. Krishnan), but it is not an official joint statement representing the two bodies.

HOW DOES SMART WORK? RATIONALE AND MECHANISM OF ACTION

Whereas maintenance ICS-LABA treatment with as-needed SABA reliever improves asthma control and reduces the background risk for exacerbations compared with ICS plus as-needed SABA, the SMART approach specifically uses ICS-formoterol as both the maintenance inhaler and the reliever inhaler. It titrates additional ICS together with additional formoterol against breakthrough symptoms when symptoms prompt reliever use, which significantly reduces the risk for severe exacerbations (defined as an emergency room visit, hospitalization, or the need for systemic corticosteroids for 3 or more days)⁷ compared with maintenance ICS or ICS-LABA regimens with a SABA reliever.²⁻⁵ The benefit of SMART in reducing asthma exacerbations is thought to occur partly by providing additional anti-inflammatory treatment during the window when asthma and airway inflammation are worsening.^{8,9} In patients taking maintenance ICS or ICS-LABA, although as-needed formoterol has been shown to reduce the risk for exacerbations compared with as-needed SABA,¹⁰⁻¹² extra doses of both ICS and formoterol in SMART may contribute to a further reduction in exacerbation risk during this critical period, which may range from 1 day to several days.^{8,9,12} Even 1 day of modestly high SABA use heralds an increased risk for an attack in coming days that is reduced if the

reliever is formoterol, and it is further reduced if the reliever is budesonide-formoterol.^{8,9}

PRACTICAL POINTS FOR CLINICIANS

Does ICS-formoterol work as quickly as a SABA (eg, albuterol) for relief of symptoms and bronchoconstriction?

Rapid relief of asthma symptoms is a fundamental need for individuals with asthma. The onset of action of formoterol is as rapid as albuterol, but it has the added advantage of a longer duration of action.^{13,14} Differences in perceived benefit have been reported by some individuals using a dry powder inhaler compared with a pressurized metered-dose inhaler (pMDI) device.

What dose of ICS-formoterol should be used for SMART?

Both the 2020 NAEPP Asthma Update and the 2021 GINA report recommend prescribing SMART for adults and adolescents with low-dose maintenance ICS-formoterol in step 3 and medium-dose maintenance ICS-formoterol in step 4.^{1,2} Formulations of ICS-formoterol and recommended dose ranges of low and medium ICS doses vary among countries. Internationally, SMART is most commonly prescribed for adults and adolescents with budesonide-formoterol 160/4.5 μg delivered dose (mass of drug emitted per actuation that is actually available for inhalation at the mouth, corresponding to a metered dose of 200/6 μg , the mass of drug that is available within the inhaler per actuation). Examples of suggested doses used internationally in adults and adolescents include one inhalation of budesonide-formoterol 160/4.5 μg once daily or twice daily in step 3, and two inhalations of 160/4.5 μg twice daily in step 4, each with one inhalation of the same 160/4.5 μg delivered dose formulation taken whenever needed for symptom relief (Table I). For children aged 4 to 11 years, SMART is usually prescribed in step 3 as a budesonide-formoterol 80/4.5 μg delivered dose (100/6 μg metered dose), one inhalation once daily, with one inhalation taken as needed for symptom relief, with the potential to increase the maintenance dose to one inhalation twice daily in step 4 (Table I).

If ICS-formoterol is administered from a pMDI, should the dose for relief of symptoms be one or two inhalations?

In clinical trials and clinical practice, SMART with budesonide-formoterol has mostly been delivered in a dry powder inhaler that is unavailable in the United States. However, the efficacy and safety of SMART have also been demonstrated with budesonide-formoterol 160/4.5 μg by pMDI,¹⁶ a formulation available in the United States, and with beclometasone-formoterol 100/6 μg pMDI,¹⁷ both of which are marketed in countries outside the United States. In all SMART clinical trials, including the two studies using pMDIs,^{16,17} the as-needed dose has been one inhalation of the ICS-formoterol inhaler (ie, 4.5 μg formoterol per occasion of use), which is also the as-needed dose approved internationally for clinical practice. The rationale for recommending one inhalation per as-needed dose (even though pMDIs in the United States are approved only for two inhalations per dose to ensure dosing consistency) is the relief of symptoms and bronchoconstriction associated with one inhalation and the

TABLE I. Recommended doses of budesonide-formoterol for single maintenance and reliever therapy (SMART) based on published studies and international use

Age group	Budesonide-formoterol dose	Step 3		Step 4		Step 3 or 4 Maximum total daily inhalations*
		Maintenance dose	As-needed dose	Maintenance dose	As-needed dose	
Adults and adolescents aged ≥ 12 y	160/4.5 µg delivered dose (200/6 µg metered dose)	One inhalation twice daily or once daily	One inhalation as needed	Two inhalations twice daily	One inhalation as needed	12
Children 4–11 years [‡]	80/4.5 µg delivered dose (100/6 µg metered dose)	One inhalation once daily [‡]	One inhalation as needed	One inhalation twice daily [§]	One inhalation as needed	8

There are no SMART studies with mometasone-formoterol, but if it were used, relevant formulations would be mometasone-formoterol 100/5 µg for adults and 50/5 µg for children, with the same dosing frequencies as shown. The 200/5 µg formulation of mometasone-formoterol would not be suitable for SMART.

*Total daily inhalations equal maintenance doses plus as-needed doses. The maximum number of as-needed doses depends on the number of maintenance doses prescribed and is based on evidence of safety for the total dose of formoterol over 24 h. For example, in an adult who is receiving step 3 therapy and is prescribed a maintenance dose of one inhalation twice daily of budesonide-formoterol 160/4.5 µg delivered dose (ie, 2 inhalations/d for maintenance), the maximum recommended number of as-needed inhalations of budesonide-formoterol is 10 over 24 h.

[‡]For SMART in children aged 4 to 11 years, the 2020 National Asthma Education and Prevention Program Focused Update recommends daily low-dose inhaled corticosteroid-formoterol at step 3 and daily medium-dose inhaled corticosteroid-formoterol at step 4 as maintenance treatment 1 once or twice daily.

[§]Based on one clinical study.¹⁵

^{§§}Based on expert opinion.

potential for too-rapid escalation of the formoterol dose if two puffs were taken on every occasion of as-needed use.

How much ICS-formoterol can be taken with SMART?

The recommendation for as-needed doses of budesonide-formoterol 160/4.5 µg (200/6 µg metered dose) is to take one inhalation whenever needed for symptom relief. If symptoms persist after a few minutes, another dose can be taken, but no more than 6 doses should be taken on a single occasion (no more than four doses for children aged 4–11 years). The recommended total maximum dose that can be taken temporarily on any single day (total of maintenance plus as-needed doses) for budesonide-formoterol is 12 inhalations for age 12 years and older^{3,5,18} and eight puffs for ages 4 to 11 years¹⁵ (Table I). A maximum of 12 inhalations of budesonide-formoterol 160/4.5 (200/6 µg metered dose) on a single day corresponds to a 54 µg delivered dose of formoterol (72 µg metered dose); a maximum of eight inhalations on a single day corresponds to a 36 µg delivered dose of formoterol (48 µg metered dose). For beclometasone-formoterol 100/6 µg, the recommended maximum dose on any day is eight inhalations.

However, in clinical trials and clinical practice, patients typically used far less than this upper limit (which refers to how much could be taken temporarily on any single day). The average frequency of reliever use was not significantly different between conventional and SMART treatment and was approximately one inhalation/d,^{3,9,16,18} but these trials employed fixed maintenance dosing, with no attempt to optimize treatment by adjusting the maintenance dose. In some trials of SMART, inhaler use for relief was required on fewer than 50% of days,¹⁸ and only one or two inhalations were used on each occasion.^{9,16,18} Days with excessively high reliever use were less common with SMART than with a conventional SABA reliever.¹⁶

Can SMART be prescribed with other ICS-LABA combinations?

Almost all SMART studies have used budesonide-formoterol; one study used beclometasone-formoterol.¹⁷ Caution should be exercised in extrapolating to other ICS-LABA combinations with different pharmacologic properties and posology. The LABA must provide rapid-onset bronchodilation and a dose-response relation that safely permits multiple inhalations if needed, without side effects. The formulations used for SMART contain a low dose of formoterol (4.5 µg delivered dose [6 µg metered dose]). The higher-dose budesonide-formoterol formulation (320/9 µg delivered dose [400/12 µg metered dose]) available in some countries is not approved or recommended for SMART because the total dose of formoterol with multiple as-needed dosing would increase too rapidly.

There are also insufficient data to assess whether other ICS-formoterol combinations (eg, mometasone-formoterol pMDI 50/5 µg or 100/5 µg, which are available in the United States, and fluticasone propionate-formoterol, which is unavailable in the United States) can be used for SMART. In the United States, formulary or insurance restrictions may result in mometasone-formoterol being more accessible than budesonide-formoterol for some patients. Currently, GINA advises against assuming that results obtained with budesonide-formoterol and beclometasone-formoterol combinations will apply to other ICS-formoterol combinations.⁵ Data about the harms and benefits of mometasone-formoterol in SMART are needed.

(Example of action plan template for budesonide/formoterol.

A similar action plan could be constructed for other ICS/formoterol formulations, e.g. mometasone/formoterol)

My Asthma Action Plan	
For Single Inhaler Maintenance and Reliever Therapy (SMART) with budesonide/formoterol	
Name: _____ Date: _____ Usual best PEF: _____ L/min <i>(If used)</i>	Action plan provided by: _____ Doctor: _____ Doctor's phone: _____
Normal mode My SMART Asthma Treatment is: ☐ budesonide/formoterol 160/4.5 (12 years or over) ☐ budesonide/formoterol 80/4.5 (4–11 years) My Regular Treatment Every Day: <i>(Write in or circle the number of doses prescribed for this patient)</i> Take [1, 2] inhalation(s) in the morning and [0, 1, 2] inhalation(s) in the evening, every day Reliever Use 1 inhalation of budesonide/formoterol whenever needed for relief of my asthma symptoms I should always carry my budesonide/formoterol inhaler My asthma is stable if: - I can take part in normal physical activity without asthma symptoms AND - I do not wake up at night or in the morning because of asthma Other Instructions _____ _____	Asthma Flare-up If over a Period of 2-3 Days: - My asthma symptoms are getting worse OR NOT improving OR - I am using more than 6 budesonide/formoterol reliever inhalations a day (if aged 12 years and older) or more than 4 inhalations a day (if 4–11 years) I should: ☒ Continue to use my regular everyday treatment PLUS 1 inhalation budesonide/formoterol whenever needed to relieve symptoms ☐ Start a course of prednisolone ☐ Contact my doctor Course of Prednisolone Tablets: Take _____ mg prednisolone tablets per day for _____ days OR _____ If I need more than 12 budesonide/formoterol inhalations (total) in any day, (or more than 8 inhalations for children 4–11 years) I MUST see my doctor or go to the hospital the same day
Asthma Emergency Signs of an Asthma Emergency: - Symptoms getting worse quickly - Extreme difficulty breathing or speaking - Little or no improvement from my budesonide/formoterol reliever inhalations. If I have any of the above danger signs, I should dial _____ for an ambulance and say I am having a severe asthma attack. While I am waiting for the ambulance start my asthma first aid plan: - Sit upright and stay calm - Take 1 inhalation of budesonide/formoterol. Wait 1–3 minutes. If there is no improvement take another inhalation of budesonide/formoterol (up to a maximum of 6 inhalations on a single occasion) - If only albuterol is available, take 4 puffs as often as needed until help arrives - Start a course of prednisolone tablets (as directed) while waiting for the ambulance - Even if my symptoms appear to settle quickly, I should see my doctor immediately after a serious attack	

Modified from Australian action plan with permission from National Asthma Council Australia and AstraZeneca Australia

FIGURE 1. Example of action plan template for patients using SMART with budesonide/formoterol. See [Appendix E1](#) (available in this article's Online Repository at www.jaci-inpractice.org) for a customizable version of this action plan. A similar action plan could be constructed for patients using SMART with other inhaled corticosteroids (ICS)-formoterol formulations (eg, mometasone-formoterol). PEF, peak expiratory flow.

The combination of ICS with salmeterol, which has a slower onset of action and a flat dose-response curve, should not be used for SMART therapy. Similarly, combinations of ICS and ultra-long-acting β_2 -agonists (eg, indacaterol, vilanterol) should not be used for a SMART regimen owing to their efficacy-safety profile and potential accumulation if dosed more frequently.

Can SMART be prescribed with ICS-formoterol as a reliever and an alternative ICS-LABA as maintenance therapy?

In patients taking maintenance treatment with ICS-LABA combinations other than ICS-formoterol (eg, fluticasone propionate-salmeterol), the use of ICS-formoterol for quick relief is not recommended by either GINA⁵ or the 2020 NAEPP Asthma Update¹ because of the lack of evidence for safety or efficacy with this mixture. In addition, if two different medications are used, patients may be confused about which inhaler to use for relief.

Is SMART with ICS-formoterol safe?

The 2020 NAEPP Asthma Update advises that clinicians should inform patients that studies involving SMART have found “no difference in documented harms between this type of therapy and daily ICS-LABA.”¹ This conclusion is supported by

a pooled analysis of six randomized double-blind and seven open-label clinical trials comparing SMART with budesonide-formoterol with alternative treatment options in steps 3 and 4¹⁹ and a Cochrane review of 13 trials.³

Who should be considered for SMART treatment?

Candidates for SMART treatment should require maintenance treatment with ICS-LABA (ie, 2020 NAEPP Asthma Update or GINA 2021 steps 3 or 4). No recognized patient characteristics exclude patients from consideration for SMART. Because the main advantage of SMART is the reduction of severe exacerbations, with the associated reduction in potential cumulative adverse effects of oral corticosteroids,²⁰ SMART is particularly well-suited to those with a history of asthma exacerbations. It has not been tested specifically in individuals who are obese or in pregnant women.

In which patients may it be acceptable or preferable to continue with ICS-LABA plus as-needed SABA treatment?

Compared with ICS-LABA plus as-needed SABA, SMART may offer less added benefit for those whose symptoms are well-controlled, with no exacerbations in the recent past and no risk

TABLE II. Some messaging and practical steps when introducing patients to the single maintenance and reliever therapy (SMART) approach

Message	Practical steps
What are your goals for your asthma management? What are your concerns?	Tailor the discussion about SMART to patients' individual goals, preferences, and concerns.
Use the new (combined ICS-formoterol) reliever as you used SABA in the past.	Explain that ICS-formoterol replaces SABA completely and provides similarly rapid relief with less risk for severe exacerbations. As they did with SABA, it should be used without delay when symptoms occur. Formoterol has a longer duration of action; they might find less need for repeated use on a single day.
ICS-formoterol reduces the risk for asthma attacks.	Consider each patient's individual risk profile for severe exacerbations (eg, one or more in the past 12 mo) and address those that are modifiable. Explain the relevance of SMART to the patient's situation. ²
How much ICS-formoterol may you use as reliever in 1 day?	Advise the patient about the maximum total inhalations on any single day (Table 1: for budesonide-formoterol, a total of 12 inhalations for adults and a total of eight inhalations for children), including both maintenance and as-needed doses. Preferably provide the maintenance dose and reliever instructions in a personalized asthma action plan.
What should I do if I reach the maximum recommended number of inhalations on any day?	Advise that if the patient requires more than 12 inhalations in total in a single day (eight inhalations for children), or if symptoms worsen rapidly without expected relief from the reliever, the patient should seek medical assistance urgently (see example in Figure 1). High use (six or more inhalations) on two or more successive days may be reasonably included as a prompt to obtain medical assistance.
Keep your inhaler on hand at all times.	Ensure that patients carry the ICS-formoterol inhaler with them so they can use it for symptom relief
Continue your regular maintenance dose of ICS-formoterol. This will be reviewed periodically.	Advise about the number of maintenance doses, once or twice daily, and plan for review (Table 1); preferably record the maintenance dose in a customized asthma action plan. Reassure that day-to-day asthma symptom control should be similar with SMART, provided patients take the prescribed maintenance treatment.
Know your inhaler device.	Instruct and test inhaler technique, demonstrate the dose counter (if available), describe how to recognize when the device is empty, and emphasize storage requirements. Check that patients can use it correctly.
SMART treatment is safe. Do you have concerns?	Provide the option of a trial period of ICS-formoterol as reliever, with SABA as backup. If necessary, review safety data. Address concerns about switching from the trusted SABA reliever: various approaches may be used. Indicate clearly that the intention is for no further SABAs to be prescribed or issued once patients have made the transition. This is important, because continued access to a SABA inhaler may result in a return to its preferential use, overreliance on SABA alone, and possibly poor adherence to maintenance treatment. If faced with reluctance, the following approach may be helpful: <i>For the next while, carry both the old and new reliever with you. When you feel the need for your reliever, first try the new (combination) reliever. If it does not provide the expected effect within minutes, you have the option to resort to the SABA.</i> This simple advice usually addresses patients' initial concern and permits them to explore and experience relief from the new treatment. The SABA prescriptions may then be stopped at the next visit.
Mouth rinsing is not necessary after reliever use.	Mouth rinsing is recommended after maintenance dosing, but it is not necessary after as-needed doses. This instruction has been provided in studies of over 30,000 patients with SMART and as-needed-only treatment with budesonide-formoterol, with no increased risk for oral candidiasis compared with using SABA as the reliever. ¹⁹
Issues related to obtaining your medication.	Patients may require an initial supply of two inhalers for use in different locations. This may reduce the chance of them running out, because the second inhaler can serve as a backup while the other is replaced. How clinicians write the prescription may assist the process of obtaining more than one inhaler. For example: <i>ICS-formoterol x ...inhalations in the morning and xx inhalations in the evening every day, and ICS-formoterol 1 inhalation as needed for symptom relief. Dispense 2.</i> Clearly stating on the prescription "one for home and one for school" may also be helpful.

(continued)

TABLE II. (Continued)

Message	Practical steps
Do you require information for other caregivers, teachers, or school nurse concerning the new treatment?	Parents, other caregivers, and teachers may need to be educated about the new treatment that has replaced the more familiar SABA reliever, including inhaler technique training and advice about dosage.
Understand your instructions and action plan.	As a final step, check that the information offered to patients and caregivers has been understood. Because adherence is closely related to perception about the need for a medication and concerns about safety and/or cost, ³⁰ these aspects must be discussed at the first visit, and preferably also at subsequent visits. As with all asthma management, the limited duration of appointment times may reduce the feasibility of providing comprehensive education during routine clinic visits. The involvement of nurses, asthma educators, and trained lay educators may be helpful. An asthma action plan (Figure 1) may be used to facilitate and reinforce understanding.

ICS, inhaled corticosteroid; SABA, short-acting β_2 -agonist.

factors for exacerbations.⁵ The 2020 NAEPP Asthma Update advises that “The recommended alternate therapy of maintenance ICS-LABA along with SABA as quick-relief therapy does not need to be changed if it is providing adequate control.”¹ The GINA 2021 report states that regimens with as-needed SABA are an alternative approach if the use of ICS-formoterol reliever (including SMART in steps 3 and 4) “is not possible or is not preferred by a patient with no exacerbations on their current therapy.” However, GINA advises that “Before prescribing a regimen with SABA reliever, consider whether the patient is likely to be adherent with their ICS-containing controller therapy, as otherwise they will be at higher risk of exacerbations.”⁵

Is SMART suitable for use in ‘poor perceivers’?

Perception of changes in airway caliber and other physiologic changes in asthma vary widely among individuals with asthma and is influenced by factors such as disease severity, psychological state, age, ethnicity, and sex.²¹ Although poor perception may result in individuals delaying or underusing the reliever, poor perception is strongly associated with poor adherence with maintenance treatment and with greater emergency health care use²² and greater risk for near-fatal asthma. No studies have compared treatment modalities (including SMART) in poor perceivers; indeed, because such patients have few symptoms, they are unlikely to be included in asthma clinical trials. However, when such patients perceive the need for symptom relief, using an ICS-containing reliever as part of SMART instead of a SABA reliever may be a safer and more effective option, especially if they have been poorly adherent to the maintenance controller.²³ In all patients, assessment of asthma control should include an evaluation of risk factors for exacerbations including low lung function, and airway inflammation if it can be assessed, not just symptom control.

Will patients who use SMART reduce adherence to maintenance dosing?

In a 6-month trial of individuals with asthma and a severe exacerbation in the past year, participants randomized to SMART had fewer days without the use of ICS-LABA, or with only one dose of ICS-LABA, based on electronic inhaler monitoring. Thus, symptom-prompted treatment increased the overall exposure to an ICS-containing treatment, although it was still lower than prescribed.¹⁶ In a randomized open-label study of patients in primary care with documented poor adherence,

SMART resulted in higher use of ICS-LABA than for patients with conventional ICS-LABA plus as-needed SABA.²³

In a patient prescribed SMART, can the maintenance dose be reduced?

Once asthma is well-controlled, the maintenance dose should be adjusted to the lowest dose at which effective control of asthma is maintained. For some adults and adolescents, this can be achieved by reducing the maintenance dose to once daily. An increase in the requirement for as-needed doses after a reduction in the maintenance dose suggests that the patient should return to the previously prescribed dose. Patients should be reminded to use extra doses of ICS-formoterol when needed for symptom relief. Patients who have lower lung function may benefit from the higher maintenance dose (two inhalations twice daily), but the as-needed dose remains the same²⁴ (Table I).

Is day-to-day asthma symptom control with SMART inferior to that achieved with regular maintenance ICS-LABA plus SABA?

In studies directly comparing the two regimens, there is no evidence of significant or clinically important differences in asthma symptom control measured by a variety of methods including the Asthma Control Questionnaire.^{2,4,8} Poor or suboptimal symptom control, which also includes the need for frequent use of as-needed ICS-formoterol over the previous 4 weeks, should prompt a review of maintenance treatment. For example, from clinical experience, individuals with asthma who have taken an additional as-needed dose of ICS-formoterol almost daily (5 or 6 days/wk) over the past month may agree to a step-up of maintenance treatment.

Can budesonide-formoterol be used before exercise and replace SABA for this indication?

Pre-exercise formoterol^{25,26} or budesonide-formoterol²⁷ provides greater protection against exercise-induced bronchoconstriction than does pre-exercise SABA, but pre-exercise formoterol (alone) is no longer recommended because of concern about the risks of LABA-only treatment. A double-blind randomized controlled trial in individuals with mild asthma found that the use of low-dose ICS-formoterol for symptom relief and before exercise reduced exercise-induced bronchoconstriction at 6 weeks to an extent similar to that with regular ICS.²⁷ Based on available data, it would be

reasonable for a patient receiving SMART who needed exercise prophylaxis to take one inhalation of their ICS-formoterol inhaler before exercise.^{5,28}

However, if ICS-formoterol is unavailable, such as in a school setting, it would be acceptable to use albuterol for pre-exercise prophylaxis.

What if ICS-formoterol is unavailable in an emergency?

Currently, in the absence of an appropriate combination inhaler, albuterol could be used for rescue therapy in an emergency, such as in a school setting. Concerns about the extra expense of ICS-formoterol for rescue therapy, including in the school setting, could change in time as generic and lower-priced combination inhalers become available.

Is phenotyping based on biomarkers of type 2 inflammation necessary in selecting patients for SMART?

To date, no study has prospectively selected persons for SMART treatment on the basis of their inflammatory biomarker status. Future studies of inflammatory phenotyping for patients requiring step 3 or 4 treatment may provide insights in this regard. In a post hoc analysis of one study, beclometasone-formoterol SMART significantly reduced severe exacerbations compared with fixed-dose beclometasone-formoterol plus as-needed SABA across the continuum of baseline blood eosinophils, with a trend toward greater reduction of severe exacerbations in patients with higher baseline eosinophil counts.²⁹ More studies are needed.

What are the practical barriers to introducing SMART in the US practice setting?

There are specific barriers to using SMART in the United States. The first is that budesonide-formoterol is not currently approved by the FDA for use in a SMART regimen, and beclometasone-formoterol is not currently available in the United States. The US package insert for budesonide-formoterol recommends against its use for acute asthma and against the use of more than 4 puffs/d. However, clinical trial evidence strongly supports the use of budesonide-formoterol in SMART, and publication of the 2020 NAEPP Asthma Update, which strongly recommends SMART, is a first step in the United States towards obtaining approval for its use within government-sponsored health care agencies.

A second issue is that many US insurers will cover the cost of only a 30-day supply of maintenance medication at a time. Depending on the number of as-needed doses per month, SMART may require more than one inhaler per month. In addition, this may be problematic for children who need to have inhalers at home, in school, and perhaps in other locations (eg, childcare or after-school activities).

These issues need to be addressed. It is hoped that the strong recommendation for SMART with a high certainty of evidence in the 2020 NAEPP Asthma Update may stimulate an assessment of this indication by insurers, manufacturers, the Centers for Medicaid and Medicare, and the FDA. In the meantime, clinicians should continue to engage in shared decision-making with individual patients about potential benefits, risks, costs, and the feasibility of evidence-based treatment options.

Does as-needed ICS-formoterol involve additional cost?

There is a significant difference in the unit price of albuterol compared with ICS-formoterol formulations that may limit the uptake of SMART in some settings. Optimizing the maintenance dose of ICS-formoterol and ensuring correct inhaler technique can reduce as-needed use to none or a few occasions per week, with increased use only when exacerbations threaten. However, provision needs to be made for these additional doses when refills are required. The extra cost may be offset by savings resulting from exacerbations prevented by this method, and the long-term effects of repeated courses of systemic corticosteroids cannot be ignored.²⁰ Longer-term, real-world cost-effectiveness studies of SMART versus alternative controller-reliever regimens are needed to address this question for individual countries and health systems.

HOW DO I INTRODUCE SMART TO MY PATIENTS?

As with all treatments, high patient satisfaction and adherence with treatment are more likely to be achieved through effective communication, education, and shared decision-making.^{1,5} For patients requiring step 3 or 4 therapy, SMART provides the option of rapid symptom relief, a single medication, similar daily symptom control, reduced risk for severe exacerbations, and a lower total ICS dose.^{2,3} Prescription of more than one type of inhaler (as may occur with ICS-LABA plus as-needed SABA) is associated with a lower likelihood of adherence⁵ and a greater chance of incorrect inhaler technique. In deciding whether to recommend ICS-LABA with as-needed SABA, the patient's willingness and likelihood of adhering to a daily maintenance treatment should be considered, because poor adherence could result in the use of SABA alone.⁵

The provision of a written action plan improves outcomes in asthma and is recommended for all patients.^{5,28} In several countries, a written asthma action plan customized for SMART, originally developed in Australia, was found to be simple to complete and helpful for introducing SMART to patients. Figure 1 shows an example of such an action plan. See Appendix E1 (available in this article's Online Repository at www.jaci-inpractice.org) for a customizable version of this action plan.

Some key points for communication about SMART are provided in Table II. The approach to introducing SMART to a patient may differ between those who have newly received a diagnosis of asthma and those who currently use SABA as a reliever.

CONCLUSIONS

The SMART approach to treatment in patients requiring step 3 and 4 therapy is based on strong evidence, is recommended as the preferred treatment by both the NAEPP 2020 Focused Update and the GINA 2021 strategy report, and has been widely implemented globally for more than 15 years. Lessons learned in different practice settings provide assurance that the treatment approach can be rapidly and safely introduced to most patients and is easily learned and well-accepted by patients and caregivers. Single maintenance and reliever therapy is not a substitute for good clinical management, but it assists by reducing the risk for severe asthma exacerbations without compromising maintenance treatment and may improve long-term asthma control. It also reduces the potential for overreliance on SABAs. It is best applied with the aid of an

individualized written action plan designed for use with SMART as part of integrated asthma care, addressing symptom control, modifiable risk factors, comorbidities, education, and skills training, and with long-term monitoring and review and adjustment of the maintenance dose if needed. Specialists have an important role in educating the primary care community about SMART and in working with pharmacists and insurers to ensure a smooth transition when SMART is prescribed, but additional efforts will be needed to increase reach to primary care audiences and to patients with asthma.

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REFERENCES

- Cloutier MM, Baptist AP, Blake KV, Brooks EG, Bryant-Stephens T, et al. Expert Panel Working Group of the National Heart, Lung, and Blood Institute (NHLBI) administered and coordinated National Asthma Education and Prevention Program Coordinating Committee (NAEPCC). 2020 Focused Updates to the Asthma Management Guidelines: a report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group. *J Allergy Clin Immunol* 2020;146:1217-70.
- Sobieraj DM, Weeda ER, Nguyen E, Coleman CI, White CM, Lazarus SC, et al. Association of inhaled corticosteroids and long-acting β -agonists as controller and quick relief therapy with exacerbations and symptom control in persistent asthma: a systematic review and meta-analysis. *JAMA* 2018;3219:1485-96.
- Cates CJ, Karner C. Combination formoterol and budesonide as maintenance and reliever therapy versus current best practice (including inhaled steroid maintenance), for chronic asthma in adults and children. *Cochrane Database Syst Rev* 2013;4:CD007313.
- Demoly P, Louis R, Soes-Petersen U, Naya I, Carlsheimer A, Worth H, et al. Budesonide/formoterol maintenance and reliever therapy versus conventional best practice. *Respir Med* 2009;103:1623-32.
- Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. 2021. Accessed October 31, 2021. <https://ginasthma.org/reports>
- Israel E. Implementing the guidelines: what do you do when the rubber hits the road? *J Allergy Clin Immunol* 2020;146:1271-4.
- Reddel HK, Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med* 2009;180:59-99.
- Buhl R, Kuna P, Peters MJ, Andersson TLG, Naya IP, Peterson S, et al. The effect of budesonide/formoterol maintenance and reliever therapy on the risk of severe asthma exacerbations following episodes of high reliever use: an exploratory analysis of two randomised, controlled studies with comparisons to standard therapy. *Respir Res* 2012;13:59.
- Bousquet J, Boulet LP, Peters MJ, Magnussen H, Quiralte J, Martinez-Aguilar NE, et al. Budesonide/formoterol for maintenance and relief in uncontrolled asthma vs. high-dose salmeterol/ fluticasone [erratum appears in *Respir Med* 2008;102:937-8]. *Respir Med* 2007;101:2437-46.
- Tattersfield AE, Lofdahl CG, Postma DS, Eivindson A, Schreurs AG, Rasidakis A, et al. Comparison of formoterol and terbutaline for as-needed treatment of asthma: a randomised trial. *Lancet* 2001;357:257-61.
- Pauwels RA, Sears MR, Campbell M, Villasante C, Huang S, Lindh A, et al. Formoterol as relief medication in asthma: a worldwide safety and effectiveness trial. *Eur Respir J* 2003;22:787-94.
- Rabe KF, Aizen T, Magyar P, Larsson P, Jorup C, Lalloo UG. Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study. *Lancet* 2006;368:744-53.
- Balanag VM, Yunus F, Yang P-C, Jorup C. Efficacy and safety of budesonide/formoterol compared with salbutamol in the treatment of acute asthma. *Pulm Pharmacol Ther* 2006;19:139-47.
- Jonkers RE, Bantje TA, Aalbers R. Onset of relief of dyspnoea with budesonide/formoterol or salbutamol following methacholine-induced severe bronchoconstriction in adults with asthma: a double-blind, placebo-controlled study. *Respir Res* 2006;7:141.
- Bisgaard H, Le Roux P, Bjaer D, Dymek A, Vermeulen JH, Hultquist C. Budesonide/formoterol maintenance plus reliever therapy: a new strategy in pediatric asthma. *Chest* 2006;130:1733-43.
- Patel M, Pilcher J, Pritchard A, Perrin K, Travers J, Shaw D, et al. Efficacy and safety of maintenance and reliever combination budesonide-formoterol inhaler in patients with asthma at risk of severe exacerbations: a randomised controlled trial. *Lancet Respir Med* 2013;1:32-42.
- Papi A, Corradi M, Pigeon-Francisco C, Baronio R, Siergiejko Z, Petruzzelli S, et al. Beclometasone-formoterol as maintenance and reliever treatment in patients with asthma: a double-blind, randomised controlled trial. *Lancet Respir Med* 2013;1:23-31.
- O'Byrne PM, Bisgaard H, Godard PP, Pistolesi M, Palmqvist M, Zhu Y, Ekstrom T, et al. Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. *Am J Respir Crit Care Med* 2005;171:129-36.
- Sears MR, Radner F. Safety of budesonide/formoterol maintenance and reliever therapy in asthma trials. *Respir Med* 2009;103:1960-8.
- Price DB, Trudo F, Voorham J, Xu X, Kerkhof M, Ling Zhi Jie, et al. Adverse outcomes from initiation of systemic corticosteroids for asthma: long-term observational study. *J Asthma Allergy* 2018;11:193-204.
- Barnes PJ, Szefer SJ, Reddel HK, Chipps BE. Symptom and perception of airway obstruction in asthmatic patients: clinical implications for use of reliever medications. *J Allergy Clin Immunol* 2019;144:180-6.
- O'Loughlin SB, Levesque L, Fisher T, DeWit Y, Whitehead M, To T, et al. Health services utilization is increased in poor perceivers of bronchoconstriction and hyperinflation in asthma. *J Allergy Clin Immunol Pract* 2020;8:2643-50.
- Sovani MP, Whale CI, Osborne J, Cooper S, Mortimer K, Ekström T, et al. Poor adherence with inhaled corticosteroids for asthma: can using a single inhaler containing budesonide and formoterol help? *Br J Gen Pract* 2008;58:37-43.
- Aubier M, Buhl R, Ekstrom T, Ostinelli J, van Schayck CP, Selroos O, et al. Comparison of two twice-daily doses of budesonide/formoterol maintenance and reliever therapy. *Eur Respir J* 2010;36:524-30.
- Parsons JP, Hallstrand TS, Mastrorade JG, Kaminsky DA, Rundell KW, Hull JH, et al. An official American Thoracic Society clinical practice guideline: exercise-induced bronchoconstriction. *Am J Respir Crit Care Med* 2013;187:1016-27.
- Hermansen MN, Nielsen KG, Buchvald F, Jespersen JJ, Bengtsson T, Bisgaard H. Acute relief of exercise-induced bronchoconstriction by inhaled formoterol in children with persistent asthma. *Chest* 2006;129:1203-9.
- Lazarinis N, Jorgensen L, Ekstrom T, Bjerner L, Dahlen B, Pullerits T, et al. Combination of budesonide/formoterol on demand improves asthma control by reducing exercise-induced bronchoconstriction. *Thorax* 2014;69:130-6.
- National Asthma Education and Prevention Program. Expert Panel Report 3 (EPR-3): Guideline for the Diagnosis and Management of Asthma – Summary Report 2007. *J Allergy Clin Immunol* 2007;120:S94-138.
- Brusselle G, Nicolini G, Santoro L, Guastalla D, Papi A. Beclometasone dipropionate/formoterol maintenance and reliever therapy asthma exacerbation benefit increases with blood eosinophil level. *Eur Respir J* 2021;58:2004098.
- Murphy J, McSharry J, Hynes L, Matthews S, van Roon L, Molloy GJ. Prevalence and predictors of adherence to inhaled corticosteroids in young adults (15-30 years) with asthma: a systematic review and meta-analysis. *J Asthma* 2021;58:683-705.