

CLINICAL REVIEW

Be SMART About Asthma Management: Single Maintenance and Reliever Therapy

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Single maintenance and reliever therapy (SMART) is an asthma treatment approach that utilizes combined inhaled corticosteroids and long-acting β -agonists for maintenance and quick relief therapy. Despite the evidence for its benefits in asthma treatment and its adoption into American and international asthma guidelines and recommendations, SMART remains a practice of some debate. This article reviews the available evidence for SMART and offers guidance for its integration into comprehensive asthma management. Overall, short-acting β -agonist-only asthma therapy regimens should be avoided, regardless of condition severity (SOR A Recommendation). Family medicine clinicians should start SMART for patients requiring either GINA Step 3 or 4 therapy, especially if they have signs of poor adherence (SOR B Recommendation). Finally, use budesonide-formoterol over other inhaled corticosteroid/long-acting β -agonist combinations when implementing SMART (SOR B Recommendation). (J Am Board Fam Med 2024;37:745–752.)

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For decades, the mainstay of asthma treatment has been inhaled β -agonists and inhaled corticosteroids (ICS). Traditionally used as rescue and maintenance therapies respectively, recent data question this approach as evidence-based. β -agonists like albuterol act on adrenergic receptors, activating adenyl cyclase and preventing airway smooth muscle contraction, but do not reduce underlying causative inflammation. ICS prevent asthma exacerbation on a pathophysiologic level by reversing

capillary permeability, reducing inflammation, and reducing the risk of bronchial hypersensitivity, but offer limited acute relief. Despite these benefits, patient ICS adherence is poor, increasing the risk for exacerbation and asthma progression.⁹ Thus, the idea was born to use combination ICS/ β -agonist formulations to improve ICS exposure among patients with asthma.

Single maintenance and reliever therapy (SMART) is an asthma treatment approach using an ICS and long-acting β -agonist (LABA) for maintenance and quick relief therapy as a single inhaler.¹⁰ Through this approach, patients continue usual step-directed maintenance therapy and use additional inhalations as needed for symptom relief.⁷ Specific dosing can be found in Table 1. Nearly all current SMART data use formoterol as the LABA because it has a comparable onset of action to albuterol with a longer duration of action.^{7,11–16} The addition of ICS to relief medication within SMART is advantageous for acute therapy since asthma is an inflammatory disease by nature. While β -agonists address acute bronchoconstriction, they do not mitigate the underlying inflammatory process, putting patients at risk for disease progression. SMART is associated with reductions in severe exacerbations and potential

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Table 1. Clinical Comparisons Between SMART and Historical ICS-SABA Therapy

Regimen	Inhaler Formulation	Age Group (Years)	Dosing			Clinical Pearl
			Maintenance	Reliever	Maximum Daily Dose	
Budesonide-Formoterol (SMART)	MDI	Children 4 to 11	80-4.5 µg (1 puff) Once Daily	80-4.5 µg (1 puff) PRN	8 Inhalations	Patients do not need to rinse their mouth following as-needed inhalations
		Adults & Adolescents 12 +	160-4.5 µg (1 puff) Once or Twice Daily	160-4.5 µg (1 puff) PRN	12 Inhalations	
Budesonide & Albuterol (ICS-SABA)	Flexhaler & HFA	Children 4 to 11	180 µg (1 puff) Twice Daily (Budesonide)	180 µg (2 puffs) PRN (Albuterol)	360 µg (Budesonide)	Do not shake the Flexhaler Use both inhalers to treat acute asthma symptoms
		Adults & Adolescents 12 +	180 µg (1 puff) Twice Daily (Budesonide)	180 µg (2 puffs) PRN (Albuterol)	720 µg (Budesonide)	

Abbreviations: MDI, Metered-Dose Inhaler; HFA, Hydrofluoroalkane; PRN, As-needed; SMART, Single Maintenance and Reliever Therapy; ICS-SABA, ICS monotherapy plus short-acting b -agonists.

cumulative adverse effects of oral corticosteroids, while adding simplicity of a single inhaler.^{7,9}

Early studies for SMART were conducted in poorly controlled ICS-treated patients comparing budesonide-formoterol SMART with conventional ICS monotherapy plus short-acting β -agonists (SABA) as needed or budesonide-formoterol plus SABA as needed.¹⁷ Many studies have shown conflicting results but had design limitations, such as lack of blinding, that may have introduced bias. Later studies more consistently showed signs of improved 12-month outcomes with SMART, including improvements in morning peak expiratory flow, number of reliever-free days, time to first severe exacerbation, and asthma symptom score with severe exacerbations without significant differences in safety outcomes.¹⁷ In 2018, a meta-analysis evaluating patients with asthma demonstrated the benefits of SMART over conventional treatment with respect to exacerbation risk, sparking its formal inclusion into the Global Initiative for Asthma (GINA) Report and National Asthma Education and Prevention Program (NAEPP) guidance (Table 2).^{6,10,18} Notably, the classification of asthma severity differs between these reports. The GINA Report has shifted from using symptoms (SABA frequency, night waking, exacerbations, etc.) exhibited before controller treatment for classification (used by the NAEPP⁶) to how difficult the disease is to treat⁵:

- Mild: controlled with as-needed ICS-formoterol or low dose ICS plus as-needed SABA
- Moderate: controlled with Step 3 or 4 treatment (low or medium dose ICS/LABA)
- Severe: uncontrolled despite high dose ICS/LABA, or requires high dose ICS/LABA to maintain adequate control

In clinical practice, the term “mild asthma” should generally be avoided as it can render a false sense of complacency despite continued risk of severe exacerbations.⁵

Current guidelines advise against extrapolating the benefits of SMART using budesonide-formoterol to other ICS/LABA combinations, such as mometasone-formoterol, as similar efficacy has not been established.^{5,7,19} Notably, while ICS-formoterol for SMART is guideline-directed, it lacks formal approval by the US Food and Drug Administration (FDA) for this indication, thereby furthering confusion on its implementation.⁸ The purpose of this article is to summarize the available

Table 2. Population-Based Single Maintenance and Reliever Therapy (SMART) Recommendations

Guideline	Patient Population			ACO	EIB
	Age (Years)				
	0 to 5	6 to 11	≥12		
GINA ⁵ (2022)	Not indicated	Initiate SMART at Steps 3 & 4	Initiate SMART at Steps 3 & 4	Refer to patient age	None
	0 to 4	5 to 11	≥12	ACO	EIB
NAEPP ⁶ (2020)	Not indicated	Initiate SMART at Steps 3 & 4 May continue ICS+SABA therapy if patient is well controlled	Initiate SMART at Steps 3 & 4 May continue ICS+SABA therapy if patient is well controlled	None	None

ICS-formoterol is the preferred reliever medication in GINA Steps 1 or 2 for patients older than 12 years old and may be used to reduce exercise-induced bronchoconstriction when used as needed.

Abbreviations: GINA, Global Initiative for Asthma; NAEPP, National Asthma Education and Prevention Program; ACO, Asthma/COPD Overlap; EIB, Exercise-Induced Bronchoconstriction; SMART, Single Maintenance and Reliever Therapy; ICS-SABA, ICS monotherapy plus short-acting b-agonists.

evidence supporting SMART using ICS-formoterol formulations and facilitate the uptake of this approach to improve asthma care nationwide.

SABA-Only Therapy Is Broken, Let Us Fix It

Historically, SABA alone, most commonly albuterol, were the only quick relief therapies recommended for “mild asthma” (GINA Step 1 or 2).²⁰ However, SABA overuse, defined as using SABA more than twice weekly,¹ increases risk of asthma-related emergency department (ED) visits and asthma-related hospitalizations by 25% and 45%, respectively.² Further, SABA overuse is associated with increased risk of asthma exacerbation and overall mortality.³ Primary care clinicians should use annual and post-ED follow-up visits to discuss the risks of SABA-only regimens.

The known risks of SABA overuse, coupled with the protective effects of regular ICS use,¹ prompted updates to the GINA Report in 2019 urging to avoid SABA-only regimens for asthma treatment, which remains the current GINA recommendation.^{5,18} Instead, primary care clinicians should use symptom-driven or daily inhaled ICS-containing treatment. Unfortunately, ICS adherence has consistently been as low as <50% historically.^{1,2,4} Many patients continue to opt for SABA-only treatment and thus do not receive the protective anti-inflammatory benefits associated with consistent ICS use. Primary care clinicians should reinforce

the benefits of daily ICS to all patients with asthma and advise those taking long-standing SABA-only regimens who are hesitant to switch of the risks of SABA-only treatment. Finally, avoid initiating SABA-only therapy altogether. While not falling under the definition of SMART, GINA notably also prefers the use of ICS-formoterol as a reliever medication in patients with asthma in steps 1 or 2 (those who do not take a maintenance medication). NAEPP guidance does not do the same.^{5,6} These recommendations derive from a number of ICS-formoterol trials, investigating the use of ICS-formoterol as a reliever medication.^{11–16}

Choose SMART for Adults

Current guidance from the NAEPP and GINA (Table 2)^{5,6} recommends using ICS-formoterol for SMART over ICS monotherapy plus as needed SABA or ICS-LABA plus as needed SABA for patients with asthma in Steps 3 or 4, who are older than 4 and 5 years, respectively. Table 3^{16,21,22} outlines the evidence behind these recommendations. A 24-week open label, randomized controlled trial (RCT) conducted by Patel and colleagues compared SMART (budesonide-formoterol [200/6 µg per actuation] 2 actuations twice daily plus 1 actuation as needed for symptom relief) with standard treatment (budesonide-formoterol [200/6 µg per actuation] 2 actuations twice daily plus 1 to 2 actuations of salbutamol [100 µg per actuation] as

Table 3. Notable Trials Investigating Single Maintenance and Reliever Therapy (SMART) for Asthma

	Patel et al. ⁴	Bisgaard et al. ¹⁶
Study design	12-month, open-label RCT	12-month, double-blind RCT
Population	Adults 16 to 65 years old with: <ul style="list-style-type: none"> Asthma requiring daily ICS for maintenance, and An asthma exacerbation requiring healthcare presentation and oral corticosteroids or nebulized bronchodilator in the preceding year 	Children 4 to 11 years old with <ul style="list-style-type: none"> Asthma history ≥ 6 months, and At least one clinically important asthma exacerbation in the past 12 months
SMART components	Budesonide-formoterol (200/6 μg per actuation) 2 actuations twice daily plus 1 actuation as needed for symptom relief	Budesonide-formoterol 80/4.5 μg daily plus additional doses for symptom relief
Comparator(s)	Budesonide-formoterol (200/6 μg per actuation) 2 actuations twice daily plus 1 to 2 actuations of salbutamol (100 μg per actuation) as needed for symptom relief	<i>Fixed combination:</i> Budesonide/formoterol 80/4.5 μg daily plus terbutaline 0.4 mg for symptom relief <i>Fixed-dose budesonide:</i> Budesonide 320 μg daily plus terbutaline 0.4 mg for symptom relief
Primary outcome	Proportion of patients with at least one high-use episode of β agonist* 56% versus 45% RR 1.24; 95% CI, 0.99-1.56; $P = .058$	Time to first exacerbation $P < .001$ compared to fixed combination $P = .02$ compared to fixed-dose budesonide
Other notable reported clinical outcome(s)	Mean (S.D.) days of high use 5.1 (14.3) versus 8.9 (20.9) Relative rate 0.58; 95% CI, 0.39-0.88; $P < .01$ Number of days with zero actuations of maintenance budesonide-formoterol 23.9 (32.6) versus 33.6 (42.8) RR 0.72; 95% CI, 0.55-0.95; $P < .022$ At least 1 severe exacerbation 19% versus 33% RR 0.56; 95% CI, 0.38-0.84; $P < .004$; NNT = 8 Number of courses of oral corticosteroids per year of follow up 0.80 (2.5) versus 1.1 (1.9) Relative rate 0.58; 95% CI, 0.41-0.84; $P < .004$	Overall exacerbations <i>Fixed combination:</i> 14% versus 38% HR 0.34; 95% CI, 0.19-0.60, $P < .001$; NNT = 5 <i>Fixed-dose budesonide:</i> 14% versus 26% HR 0.49; 95% CI, 0.27-0.90, $P < .022$; NNT = 9 Exacerbations requiring medical intervention <i>Fixed combination:</i> 0.08/patient versus 0.40/patient, $P < .001$ <i>Fixed-dose budesonide:</i> 0.08/patient versus 0.28/patient, $P < .001$

* >12 actuations of budesonide-formoterol per day in SMART group and >16 actuations per day of salbutamol in comparator group.
Abbreviations: SD, standard deviation; CI, confidence interval; RCT, randomized controlled trial.

needed for symptom relief) in 303 patients aged 16 to 65 years old with asthma requiring daily ICS for maintenance and with an asthma exacerbation requiring health care presentation and oral corticosteroids or nebulized bronchodilator in the preceding year.²¹ No statistical differences were observed between groups for the rate of 1 high-use episode (>12 total daily actuations in the SMART group and >16 daily actuations of salbutamol in the standard group). Patients in the SMART group exhibited significantly fewer mean days of high use and fewer number of days with zero actuations of maintenance budesonide-formoterol. In addition, fewer patients in the SMART group had at least 1 severe exacerbation (NNT = 8) and the number of courses of oral corticosteroids per year of follow up was significantly fewer in the SMART group. This study highlights that SMART not only is as safe as historic asthma treatment

approaches but also exhibits greater benefit. SMART provides a treatment approach that addresses the risks of SABA-only therapy and the need to increase ICS exposure while simplifying regimens, improving asthma control, and reducing exacerbations.²¹

Choose SMART for Children

The benefits of SMART in adults are clear, but asthma often affects children in whom potential dangers of corticosteroids exist. Bisgaard et al.¹⁶ conducted a 12-month, double-blind RCT comparing SMART (budesonide-formoterol 80/4.5 μg daily plus additional doses for symptom relief) with fixed combination (budesonide/formoterol 80/4.5 μg daily plus terbutaline 0.4 mg for symptom relief) and fixed-dose budesonide (budesonide 320 μg daily plus terbutaline 0.4 mg for symptom relief) in 341 children ages 4 to

11 years with asthma history ≥ 6 months and at least 1 clinically important asthma exacerbation in the past 12 months (Table 3). Participants in the SMART group experienced longer time to first exacerbation ($P < .001$ compared with fixed combination, and $P = .02$ compared with fixed-dose budesonide) and significantly fewer exacerbations overall compared with the fixed combination (NNT = 5) and fixed-dose budesonide (NNT = 9) groups. Participants in the SMART group also experienced fewer exacerbations requiring medical intervention.¹⁶ This research supports the safety and efficacy of SMART in children as young as 4 years old with a history of at least 1 asthma exacerbation.

Exercise-Induced Bronchoconstriction

While SMART may be beneficial in asthma treatment, there is limited data for its use in exercise-induced bronchoconstriction (EIB). A single study in patients >12 years old with EIB showed as needed budesonide-formoterol reduced EIB more than as needed terbutaline alone.²² In addition, combined budesonide-formoterol was noninferior to maintenance budesonide plus as needed terbutaline while exposing participants to significantly lower doses of ICS.²² Further research is needed to fully assess the appropriateness of SMART for EIB. As such, primary care clinicians may offer SABA-only or low dose ICS-formoterol reliever therapy for EIB as a part of patient-centered treatment discussions.⁵

When Asthma and Chronic Obstructive Pulmonary Disease (COPD) Overlap

Asthma-COPD overlap (ACO) characterizes patients who have persistent airflow restriction in combination with other clinical features of asthma and COPD like significant reversibility and reduced capacity for lung carbon monoxide diffusion, respectively.⁵ Differentiating between asthma and COPD in patients with long-standing asthma exhibiting persistent airflow limitation can be challenging, especially if other risk factors for COPD, such as smoking, are present. Data suggest that ACO is a disease with a distinct genetic architecture that may show higher response to ICS/LABA than other COPD phenotypes.²³ However, the Global Initiative for Chronic Obstructive Lung Disease “GOLD” 2023 Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive

Pulmonary Disease does not recognize ACO, but rather classifies asthma and COPD as distinct disorders with common symptoms that may coexist in an individual patient. These guidelines suggest primarily following asthma guidelines in these patients. Newly diagnosed patients with COPD and concurrent asthma using ICS/LABA had a decreased risk of COPD hospitalizations and death versus LABA alone.²⁴ Separately, patients aged ≥ 66 years with COPD or asthma had decreased morbidity and hospitalizations if treated with ICS alone or in combination.²⁵ As such, consider SMART built on ICS plus LABA and/or LAMA for initial ACO treatment.^{5,23}

Additional Considerations

Adherence

Poor adherence to pharmacotherapy and limited access to care can increase rates of asthma exacerbations and urgent care or ED visits.²⁶ Despite the aforementioned benefits, patient adherence to ICS is underwhelming.⁴ By incorporating ICS into maintenance and quick relief therapy, SMART improves ICS utilization. Sovani et al. conducted a 6-month, open label RCT comparing maintenance budesonide plus as needed SABA with SMART (budesonide-formoterol 200/6 μg 1 puff once daily and as required) in patients aged 18 to 70 years with clinically diagnosed asthma, currently prescribed 400 to 1000 $\mu\text{g}/\text{day}$ of beclomethasone dipropionate or equivalent with poor adherence ($<70\%$ of expected ICS prescriptions over the year prior). Participants in the SMART group showed increased cumulative budesonide doses than those assigned to as needed SABA (448 vs 252 $\mu\text{g}/\text{day}$; 95% CI, 113 to 279) and were less likely to withdraw from the study (3 vs 13; $P < .01$).¹⁵ Therefore, primary care clinicians can use SMART to improve ICS adherence in those struggling with daily ICS use.

Cost

Asthma costs the US \$81.9 million annually (2008–13) in lost time from missed school or work, ED or urgent care visits, and hospitalizations.²⁷ SABA overuse further increases costs to the health care system.^{2,28} Administrative claims data show that each additional SABA fill is associated with a 10.8% increase in all-cause costs and a 34.6% increase in asthma-related costs.²⁸ Recent data from Colombia demonstrated that SMART was nearly twice as cost-effective as budesonide-formoterol plus as

needed SABA in direct medical costs in patients 5 to 11 years old (2139.60 USD vs 4198.60 USD per year, respectively).²⁹

Further, as aforementioned, ICS-formoterol is currently not FDA-approved as reliever therapy or SMART despite being guideline-directed.⁸ Therefore, it is also not routinely covered by insurance. Patients who use ICS-formoterol both daily and as needed may require more than 1 inhaler per month and require earlier fills than allowed by payers.

Asthma Action Plans

A main component of asthma management, asthma action plans (AAPs) are formalized documents that help patients self-manage their asthma and improve outcomes.³⁰ AAPs detail maintenance therapy and explicitly outline steps for patients to self-manage flare-ups and recognize exacerbations requiring emergency care.³⁰ Primary care clinicians starting or transitioning patients with asthma to SMART should update AAPs accordingly (Figure 1).


Current Challenges and Future Directions

Because SMART studies have been conducted almost exclusively via combined budesonide/formoterol,

the utility of SMART using other ICS/ β -agonist inhalers is challenging and not recommended. Following the inclusion of SMART as well as the use of ICS-formoterol for symptom relief (steps 1 or 2) into asthma guidelines, the MANDALA and DENALI studies investigated the safety and effectiveness of budesonide-albuterol for asthma symptom relief. These phase-3 RCTs compared fixed-dose combinations of albuterol-budesonide (180-160 μ g) [HD-AB], and (180-80 μ g) [LD-AB] with budesonide alone (160 μ g) [BO], and albuterol alone (180 μ g) [AO].^{31,32} Participants in the HD-AB group showed significantly lower risk of severe asthma exacerbation than those in the AO group (HR 0.74; 95% CI, 0.62-0.89). However, the hazard ratio between the LD-AB and AO groups was statistically insignificant, 0.84 (95% CI, 0.71-1.00).³¹ Patients receiving fixed dose budesonide-albuterol experienced greater increases in forced expiratory volume in 1 second (FEV1) at 12-weeks. As this product pursues market entry as reliever therapy, we must continue to evaluate the appropriateness of all ICS/ β -agonist formulations for use in SMART.

In addition, more data are necessary to assess the long-term risks of SMART. Early studies showed

Figure 1. Allergy & Asthma Network SMART Asthma Action Plan.³³

 (Example of action plan template for budesonide/formoterol. A similar action plan could be constructed for other ICS/formoterol formulations, eg, mometasone/formoterol)

My Asthma Action Plan
For Single Inhaler Maintenance and Reliever Therapy (SMART) with budesonide/formoterol

Name: _____ Action plan provided by: _____
Date: _____ Doctor: _____
Usual best PEF: _____ L/min (if used) Doctor's phone: _____

Normal mode	Asthma Flare-up	Asthma Emergency
<p>My SMART Asthma Treatment is:</p> <ul style="list-style-type: none"><input type="checkbox"/> budesonide/formoterol 160/4.5 (12 years or older)<input type="checkbox"/> budesonide/formoterol 80/4.5 (4-11 years) <p>My Regular Treatment Every Day:</p> <p>(Write in or circle the number of doses prescribed for this patient)</p> <p>Take [1, 2] inhalation(s) in the morning and [0, 1, 2] inhalation(s) in the evening, every day</p> <p>Reliever</p> <p>Use 1 inhalation of budesonide/formoterol whenever needed for relief of my asthma symptoms</p> <p>I should always carry my budesonide/formoterol inhaler</p> <p>My asthma is stable if:</p> <ul style="list-style-type: none">I can take part in normal physical activity without asthma symptomsANDI do not wake up at night or in the morning because of asthma <p>Other Instructions</p> <p>_____</p> <p>_____</p>	<p>If over a Period of 2-3 Days:</p> <ul style="list-style-type: none">My asthma symptoms are getting worse OR NOT improvingORI am using more than 6 budesonide/formoterol reliever inhalations a day (if aged 12 years or older) or more than 4 inhalations a day (if aged 4-11 years) <p>I should:</p> <ul style="list-style-type: none"><input type="checkbox"/> Continue to use my regular everyday treatment PLUS 1 inhalation budesonide/formoterol whenever needed to relieve symptoms<input type="checkbox"/> Start a course of prednisolone<input type="checkbox"/> Contact my doctor <p>Course of Prednisolone Tablets:</p> <p>Take _____ mg prednisolone tablets per day for _____ days OR</p> <p>_____</p> <p>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.</p>	<p>Signs of an Asthma Emergency:</p> <ul style="list-style-type: none">Symptoms getting worse quicklyExtreme difficulty breathing or speakingLittle or no improvement from my budesonide/formoterol reliever inhalations <p>If I have any of the above danger signs, I should dial _____ for an ambulance and say I am having a severe asthma attack.</p> <p>While I am waiting for the ambulance start my asthma first aid plan:</p> <ul style="list-style-type: none">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

that short-term SMART use was associated with significant increases in sputum and biopsy eosinophilia at 1-year, possibly indicating an inflammatory risk over prolonged use.¹⁷ It is important to continue to evaluate and compare guideline-directed therapies as new medications enter the market.

Conclusion

Although a significant shift from traditional asthma management, SMART is a safe and effective asthma treatment approach. Primary care clinicians should not delay starting or transitioning patients aged 4 years or older with asthma requiring a daily maintenance treatment. Despite its effects on immediate symptom relief, SABA-only treatment does not prevent disease progression and should be avoided. Patients receiving ICS-formoterol show improved asthma control and ICS adherence and reduced risk of severe exacerbation over a 12-month period. Long-term data are currently lacking for the risks and benefits of SMART. With new data emerging, it is possible that guidance regarding proper SMART will evolve in the coming years.

To see this article online, please go to: <http://jabfm.org/content/37/4/745.full>.

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