A Call for the United States to Accelerate the Implementation of Reliever Combination Inhaled Corticosteroid–Formoterol Inhalers in Asthma

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Asthma is a common respiratory disease that chronically affects approximately 330 million people worldwide and 30 million people in the United States (1–3). Despite its high prevalence, asthma is underdiagnosed and undertreated, particularly among patients residing in lower-income communities (4). Most (approximately 96%) of the 250,000 annual asthma deaths occur in low-income countries in which access to health practitioners and effective treatments, particularly maintenance inhalers, is sparse (3, 5). Furthermore, even in high-income countries, racial and ethnic minorities and lower socioeconomic status households continue to disproportionally experience asthma morbidity and mortality (6–9).

Although new knowledge regarding the complex pathophysiology underpinning asthma has led to the recent development of novel therapeutics in severe asthma, most patients with mild/moderate asthma have experienced few, if any, improvements in exacerbation risk and symptom control recently (10–12). To make meaningful progress for most patients with asthma, improvement in access and adherence to the backbone of asthma treatment, an inhaled corticosteroid (ICS)-containing treatment, is required (13–15). Unfortunately, in the United States, high inhaler costs and poor maintenance ICS adherence remain widespread challenges (16–18). The reasons for these challenges are likely numerous, including continuous introduction by pharmaceutical companies of new and expensive inhalers, patient reluctance to use corticosteroid-containing medications when well, and the episodic nature of asthma itself, wherein patients often deem regular maintenance inhaler adherence simply unnecessary.

Rationale for New Inhaler Paradigms in Asthma

Beginning about 20 years ago, asthma researchers started evaluating new inhaler paradigms because of a desire to develop an effective inhaler approach that would better align with many patients' real-world behaviors and preferences for reliever therapy rather than adherence to maintenance therapy (19). Furthermore, researchers began exploring new inhaler approaches partially because of trials that demonstrated reductions in severe exacerbations with reliever formoterol usage compared with short-acting β_2 agonist

(Received in original form September 13, 2022; accepted in final form December 19, 2022)

*Co–first authors.

Supported by grants from the American Lung Association (ALA) (Early Career Investigator Award) and the NIH (KL2-TR002346 [J.G.K.] and UL1-TR002345). The content is solely the responsibility of the authors and does not represent the official views of either the NIH or the ALA.

Author Contributions: J.G.K., J.K.G., M.C., and F.D.M. conceived this article, with M.C. and F.D.M. serving as senior authors. J.G.K. and J.K.G. wrote the first draft. All authors revised the draft critically for intellectual content and provided approval of the final manuscript version in its entirety.

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This article has a related editorial.

Am J Respir Crit Care Med Vol 207, Iss 4, pp 390–405, Feb 15, 2023

Originally Published in Press as DOI: 10.1164/rccm.202209-1729PP on December 20, 2022
Internet address: www.atsjournals.org

(SABA) in patients on (20, 21) or not on (20) concomitant maintenance ICS-containing treatment.

Because of subsequent concerns about the risks of long-acting β-agonist (LABA)–only treatment, these studies were followed by studies with combination budesonide–formoterol as a reliever, on top of maintenance budesonide–formoterol (i.e., the first studies of single maintenance and reliever therapy, which is often referred to as SMART [Single Maintenance and Reliever Therapy] or MART [Maintenance and Reliever Therapy] were started). Because of the significant reduction in risk of severe exacerbations with SMART compared with the same or higher-dose ICS or ICS–LABA with reliever SABA (22), a similar concept of reliever-only combination ICS–formoterol usage was subsequently investigated in mild asthma (23–26). These studies demonstrated that reliever usage of ICS–formoterol led to a large reduction in severe exacerbations and emergency department visits/hospitalizations compared with SABA monotherapy (24, 26). Further studies have examined reliever ICS–SABA usage in patients with mild asthma, either in combination (27) or as two separate inhalers (28–30), and recently in patients with moderate–severe asthma (31).

The investigation of new inhaler approaches also followed numerous observational studies demonstrating that SABA overuse is both common and associated with excess asthma morbidity and mortality (32–41). Because β agonists lack antiinflammatory properties, high usage of SABAs alone does not ameliorate airway inflammation. Furthermore, on the basis of some (but not all) studies, even short-term regular use of a SABA without a concurrent ICS results in increased airway inflammation and increased airway hyperresponsiveness because of tachyphylaxis from airway β adrenoceptor downregulation (42–46). Historically, spikes in asthma mortality have been observed after the introduction of inhalers with high-dose adrenergic agents with low β_2 selectivity, such as isoproterenol and fenoterol (47). Data from the Salmeterol Multicenter Asthma Research Trial demonstrated that salmeterol (a LABA), uncoupled to an ICS, is associated with an increased mortality risk (47, 48). This finding ultimately resulted in an FDA (U.S. Food and Drug Administration) boxed warning. However, notably, repeated large clinical trials have demonstrated the safety of LABAs when used in combination with an ICS (which has resulted in a clear statement from the FDA of ICS–LABA safety, whereas LABA monotherapy remains discouraged) (49, 50). The findings regarding the risk of β-agonist monotherapy serve in stark contrast to findings with ICS inhalers, in which underuse, rather than overuse, is associated with exacerbations and mortality (35, 36, 51, 52).

Notably, newly explored strategies that universally couple an ICS with a reliever β agonist are also believed to potentially combat the so-called SABA paradox in asthma (42). The SABA paradox recognizes that adherence to a SABA during episodes of poor asthma control is reinforced by quick symptomatic relief, whereas this behavioral reinforcement does not exist for maintenance ICS inhalers. Thus, during periods of high symptoms (with presumably increasing airway inflammation and risk of impending exacerbation), patients often increase their SABA usage but may or may not choose to use their ICS-containing inhaler (assuming they even have one), which does not ameliorate airway inflammation when theoretically most beneficial (Figure 1) (53–56).

Formoterol Is a Unique Long-acting β agonist That Allows for Reliever Usage

When exploring options to combine an ICS with a β agonist for symptom relief, a fundamental requirement is that the β agonist component quickly relieves symptoms. One option to achieve this goal is to instruct patients to actuate a separate ICS inhaler whenever using their reliever SABA. This option, however, requires patients to fill, carry, then actuate two separate inhalers when symptomatic. Combining an ICS with albuterol in a single reliever device is being increasingly explored (31). However, the option that has been most explored involves using formoterol in combination with an ICS as a reliever. Formoterol is a unique LABA that has an onset of action that is similar to albuterol itself (57, 58), provides a longer duration of action, and, perhaps most notably, allows for the potential simplicity of using the same inhaler for both maintenance and reliever usage (i.e., SMART) if indicated (59).

When considering updated asthma approaches, providers should carefully note formoterol's placement in them. Every study of SMART has used ICS–formoterol, which also has a dose–response relationship that safely allows for repeated inhalations if necessary (60, 61). Other non–formoterol-containing ICS–LABAs have different pharmacologic and posologic properties and have not been explored with SMART. All but one study (61) with as-needed ICS–formoterol has used budesonide–formoterol. A mometasone–formoterol combination is commercially available in the United States; although data about the safety and efficacy of its use in SMART are needed (59, 62), the potential use of mometasone–formoterol in SMART is supported by indirect evidence from the results of studies using budesonide–formoterol or beclomethasone–formoterol.

Reliever-only Use of ICS–Formoterol in Mild Asthma

In adults and adolescents with mild asthma, large randomized controlled trials have shown that using low-dose budesonide–formoterol as a reliever-only treatment reduces the occurrence of severe exacerbations by almost two-thirds compared with SABA monotherapy and reduces severe exacerbations requiring emergency department visits or hospitalizations by one-third compared with traditional maintenance ICS plus reliever SABA therapy (23–28, 63, 64) (Table 1). In the large SYGMA-1 (Symbicort Given as Needed in Mild Asthma) trial, among patients previously taking an ICS or leukotriene receptor antagonist, reliever use of budesonide–formoterol inhaler resulted in 63% fewer severe asthma exacerbations (rate ratio 0.37, 95% confidence interval [CI], 0.25–0.54) than reliever SABA use alone, with a number needed to treat to prevent a severe exacerbation of only 13 (65). Finally, in two pragmatic randomized controlled trials (PRACTICAL [PeRsonalised Asthma Combination Therapy with Inhaled Corticosteroid And

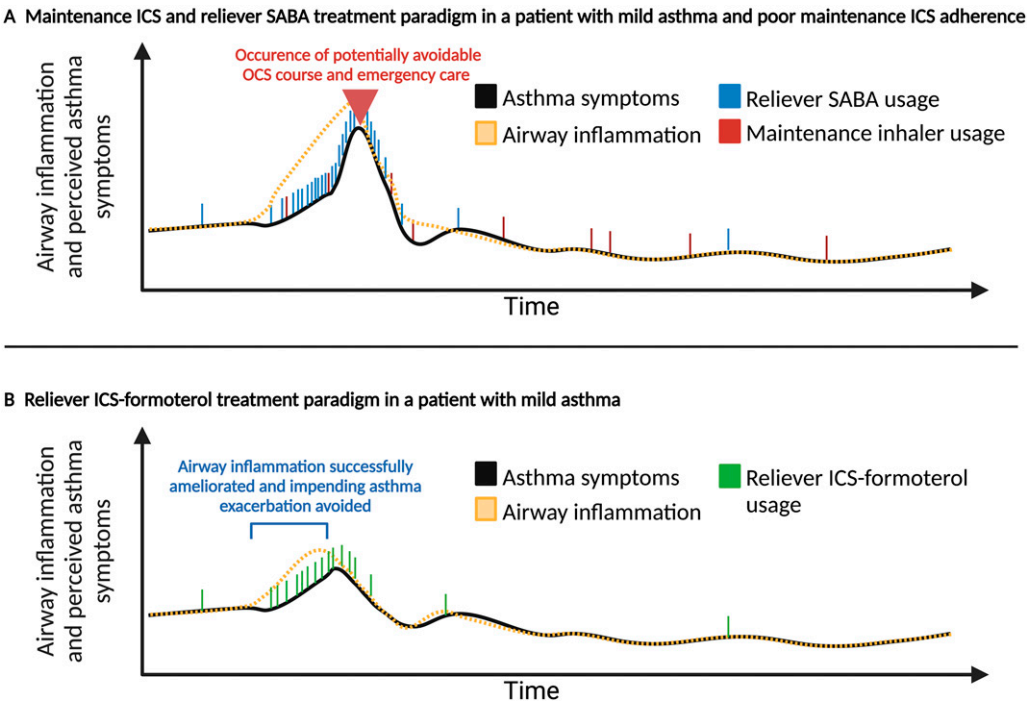

Figure 1. Hypothetical illustration of asthma symptoms and underlying airway inflammation in two different inhaler paradigms in a representative patient who is nonadherent to maintenance inhaled corticosteroid (ICS)-containing inhaler therapy. (*A*) The hypothetical first patient has suboptimal maintenance ICS adherence (red dash) throughout time and relies on increasing SABA usage (blue dash) when symptomatic, whereas (*B*) the second patient is using a reliever inhaler that contains an ICS and formoterol (green dash). As asthma symptoms (black line) and underlying airway inflammation (dashed yellow line) increase, hypothetical patient B uses increasing amounts of ICS (contained in the reliever inhaler) and is able to avert an impending serious asthma exacerbation requiring oral corticosteroids by treatment of airway inflammation. Illustration partially adapted for this manuscript from Larson and colleagues (141). OCS = oral corticosteroid; SABA = short-acting β_2 agonist.

fast-onset Long-acting β agonist] and Novel START [Novel Symbicort Turbuhaler Asthma Reliever Therapy]), a reliever-only budesonide–formoterol treatment approach was more beneficial than traditional maintenance ICS plus reliever SABA at preventing severe asthma exacerbations (23, 26).

In mild asthma, a reliever-only ICS–formoterol approach leads to lower cumulative inhaled corticosteroid exposure than traditional maintenance ICS plus reliever SABA therapy. Nevertheless, using the reliever-only budesonide–formoterol approach (as compared with maintenance ICS and reliever SABA) may lead to more day-to-day asthma symptoms for some patients. However, the difference in asthma symptoms between these approaches on the basis of the ACQ-5 (Asthma Control Questionnaire) was only 0.15 (minimal clinically important difference of the ACQ-5 is 0.50); furthermore, in clinical practice, unlike in the SYGMA studies (24, 25), patients can use ICS–formoterol prophylactically, including before exercise, to prevent symptoms from occurring (63).

SMART in Moderate/Severe Asthma

In moderate/severe asthma, a SMART approach instructs patients to use a combination ICS–formoterol inhaler on a maintenance and reliever basis. One should note that SMART is thus different from the aforementioned concept of reliever-only usage of ICS–formoterol in mild asthma. SMART has shown clear superiority to traditional inhaler management paradigms in numerous randomized trials enrolling more than 20,000 patients over the last 20 years (Table 2) (22, 54, 66–75). A recent meta-analysis showed that simply switching a patient with uncontrolled moderate/severe asthma to SMART (as opposed to stepping up maintenance ICS dosage) resulted in a prolonged time to first severe exacerbation and an approximately 30% lower risk of a future severe exacerbation (hazard ratio, 0.71; 95% CI, 0.52–0.97) (76). Notably, most studies of SMART (and all large studies of reliever-only budesonide–formoterol in mild asthma) used a dry-powder delivery device rather than a U.S.-available metered dose inhaler (MDI), which can affect the airway delivery of active medication (77, 78). However, the safety and efficacy of SMART have also been demonstrated with U.S.-available budesonide–formoterol 160/4.5 μg MDI in one study (70). Although nearly all of the evidence supporting the benefits of SMART only enrolled patients at least 12 years old (60), SMART with ultra-low–dose budesonide–formoterol (80/4.5 μg one puff daily and for symptoms) was investigated in children (age 4–11 yr) and significantly reduced the rate of exacerbations in this population (79).

Table 1. Representative Randomized Controlled Trials in Mild Asthma of Reliever Inhaled Corticosteroid–Formoterol Therapy versus Traditional Maintenance Inhaled Corticosteroid + Reliever Short-acting β_2-agonist Therapy versus Reliever Short-acting β_2-agonist Alone Therapy

Trial Name	Trial Design	Primary Inclusion Criteria	Participants (*n*)	Treatment Arms	Primary Outcome	Conclusions
SYGMA 1 (NEJM 2018) (24)	Double-blinded, multicenter, parallel-group RCT over 52 wk	⩾12 yr old, mild asthma, deemed to warrant GINA 2012 step 2 therapy; two strata: asthma uncontrolled on SABA alone or controlled on ICS or LTRA	3,849	1. Twice-daily placebo + reliever SABA 2. Twice-daily placebo + reliever budesonide–formoterol (200/6 μg)* 3. Twice-daily budesonide (200 μg) + reliever SABA	Weeks with well-controlled asthma: 1. Reliever budesonide–formoterol vs. reliever SABA alone (34.4% vs. 31.1% of wk; OR, 1.14; 95% CI, 1.00–1.30; $P = 0.046$) 2. Reliever budesonide–formoterol vs. twice-daily budesonide + reliever SABA (34.4% vs. 44.4% of wk; OR, 0.64; 95% CI, 0.57–0.73)	1. On the basis of weeks with asthma control, reliever budesonide–formoterol was superior to reliever SABA alone but inferior to twice-daily budesonide + reliever SABA therapy. 2. On the basis of the rate of severe exacerbations, reliever budesonide–formoterol was superior to reliever SABA alone but equivalent to maintenance budesonide + reliever SABA therapy. 3. Reliever budesonide–formoterol had lower ICS exposure than maintenance budesonide + reliever SABA therapy.
SYGMA 2 (NEJM 2018) (25)	Double-blinded, multicenter, parallel-group RCT over 52 wk	⩾12 yr old, mild asthma, deemed to warrant GINA 2012 step 2 therapy; two strata: asthma uncontrolled on SABA alone or controlled on ICS or LTRA	4,215	1. Twice-daily placebo + reliever budesonide–formoterol (200/6 μg) only* 2. Twice-daily budesonide (200 μg) + reliever SABA	Annualized rate of severe exacerbations: Reliever budesonide–formoterol vs. twice-daily budesonide + reliever SABA (0.11 vs. 0.12 severe exacerbations/yr; rate ratio, 0.97; upper one-sided 95% confidence limit, 1.16)	1. On the basis of the rate of severe exacerbations, reliever budesonide–formoterol was noninferior to maintenance budesonide + reliever SABA. 2. Reliever budesonide–formoterol had lower ICS exposure than maintenance budesonide + reliever SABA therapy.
PRACTICAL (Lancet 2019) (23)	Open-label, pragmatic, multicenter, parallel-group RCT over 52 wk	18–75 yr old, provider-diagnosed asthma, prescribed reliever SABA ± low–moderate maintenance ICS; deemed to warrant GINA 2014 step 2 therapy	885	1. Reliever budesonide–formoterol (200/6 μg) only* 2. Twice-daily budesonide (200 μg) + reliever SABA	Annualized rate of severe exacerbations: Reliever budesonide–formoterol vs. twice-daily budesonide + reliever SABA (0.12 vs. 0.17 severe exacerbations/yr; relative rate, 0.69; 95% CI, 0.48–1.00; $P = 0.049$)	1. In an open-label pragmatic trial, on the basis of the rate of severe exacerbations, reliever budesonide–formoterol only was superior to maintenance budesonide + reliever SABA therapy. 2. Reliever budesonide–formoterol had lower ICS exposure than maintenance budesonide + SABA therapy.

(*Continued*)

Table 1. (*Continued*)

Trial Name	Trial Design	Primary Inclusion Criteria	Participants (*n*)	Treatment Arms	Primary Outcome	Conclusions
Novel START (NEJM 2019) (26)	Open-label, pragmatic, multicenter, parallel-group RCT over 52 wk	18–75 yr old, provider-diagnosed asthma, prescribed as-needed SABA; deemed to warrant GINA 2014 step 2 therapy	668	1. Twice-daily placebo + reliever SABA 2. Twice-daily placebo + reliever budesonide–formoterol (200/6 μg)* 3. Twice-daily budesonide (200 μg) + reliever SABA	Annualized rate of exacerbations: 1. Reliever budesonide–formoterol vs. reliever SABA alone (0.20 vs. 0.40 severe exacerbations/yr; relative rate, 0.49; 95% CI, 0.33–0.72) 2. Reliever budesonide–formoterol vs. twice-daily budesonide + reliever SABA (0.20 vs. 0.18 severe exacerbations/yr; relative rate, 1.12; 95% CI, 0.70–1.79)	1. On the basis of the rate of exacerbations, reliever budesonide–formoterol was superior to SABA alone but equivalent to maintenance budesonide + reliever SABA therapy. 2. On the basis of the rate of severe exacerbations, as-needed budesonide–formoterol was superior to reliever SABA alone and maintenance budesonide + reliever SABA therapy.

Definition of abbreviations: CI = confidence interval; GINA = Global Strategy for Asthma Management and Prevention; ICS = inhaled corticosteroid inhaler; LTRA = leukotriene receptor antagonist; Novel START = Novel Symbicort Turbuhaler Asthma Reliever Therapy; OR = odds ratio; PRACTICAL = PeRsonalised Asthma Combination Therapy with Inhaled Corticosteroid And fast-onset Long-acting β agonist; RCT = randomized controlled trial; SABA = short-acting β_2 agonist; SYGMA = Symbicort Given as Needed in Mild Asthma. Throughout multiple RCTs totaling approximately 10,000 adolescents and adults with asthma, reliever use of an ICS–formoterol has shown superiority to reliever SABA monotherapy and equivalence (or superiority) with traditional maintenance ICS + reliever SABA therapy.
*The 200/6 μg budesonide–formoterol dose used in these trials corresponds to a 160/4.5 μg delivered dose (mass of drug emitted per actuation that is available for inhalation at the mouth); however, each of these trials used a dry powder inhaler that is unavailable in the United States.

Asthma Recommendations Call for Preferential Usage of Reliever ICS–Formoterol Inhalers in Mild Asthma (GINA [Global Initiative for Asthma]) and Usage of SMART in Moderate/Severe Asthma (GINA and NAEPP [National Asthma Education and Prevention Program])

Recognizing new data, committees from both GINA and the NAEPP recently updated their recommendations by deemphasizing reliever β-agonist usage without concomitant ICS (80–82). GINA has moved more aggressively than the NAEPP by preferentially recommending reliever ICS–formoterol usage at steps one and two of therapy, with the addition of maintenance ICS–formoterol SMART in step three, then higher maintenance doses for steps four and five (Figure 2) (62). In its latest iteration, the NAEPP 2020 update did not examine the evidence for reliever-only ICS–formoterol usage or unopposed reliever SABA use at step one of therapy, and so its recommendations at steps one and two were retained in the most recent update (62, 64). However, the NAEPP now alternatively recommends low-dose ICS accompany reliever SABA use at step two and escalating SMART as the preferred option at steps three and four (Figure 3).

Although differences between recommendations are highlighted, the GINA and NAEPP recommendations are more similar than discordant. Both committees have rethought inhaler recommendations in asthma altogether while clearly advocating for SMART. Importantly, the NAEPP committee's objectives were set before most of the reliever ICS–formoterol efficacy data in mild asthma emerged (80, 83, 84). GINA's decision to recommend against SABA-only therapy in step one is on the basis of evidence of ICS–formoterol efficacy in patients with symptoms as infrequently as twice per month and because starting treatment with SABA may behaviorally train patients to regard it as their main asthma therapy (26, 62, 85).

A Potential Role for Implementation Science

Unfortunately, establishing scientific evidence of efficacy and effectiveness is insufficient to ensure subsequent real-world

Table 2. Representative Randomized Controlled Trials in Moderate-to-Severe Asthma of Maintenance Therapy + Reliever Inhaled Corticosteroid–β-agonist Therapy versus Maintenance Therapy + Reliever β_2-agonist Therapy

Trial Name	Trial Design	Primary Inclusion Criteria	Participants (*n*)	Treatment Arms	Primary Outcome	Conclusion(s)
SMILE (Lancet 2006) (66)	Double-blinded, multicenter, parallel-group RCT over 12 mo	⩾12 yr old with asthma and ⩾1 exacerbation in the prior yr, pre-BD FEV_1 50–100% with ⩾12% reversibility, received ICS for 3 mo before entry yet remained symptomatic	3,394	Budesonide–formoterol (160/4.5 μg) twice-daily + reliever: 1. SABA 2. Formoterol (4.5 μg), or 3. Budesonide–formoterol (160/4.5 μg)	Time to first severe exacerbation: SMART therapy with reliever budesonide–formoterol resulted in a longer time to first severe exacerbation than twice-daily budesonide–formoterol and reliever SABA ($P = 0.005$; log-rank test) or reliever formoterol ($P = 0.005$)	1. On the basis of time to first exacerbation, SMART therapy was superior to maintenance budesonide–formoterol with reliever SABA or reliever formoterol. 2. SMART therapy with reliever budesonide–formoterol resulted in a 48% reduction in the rate of severe exacerbations compared with the same maintenance therapy with reliever SABA usage.
COMPASS (IJCP 2007) (67)	Double-blinded, multicenter, parallel-group RCT over 6 mo	⩾12 yr old with asthma and ⩾1 exacerbation in the prior yr, pre-BD FEV_1 50–100% with ⩾12% reversibility, received ICS for 3 mo before entry yet remained symptomatic	3,335	1. SMART therapy with maintenance budesonide–formoterol (160/4.5 μg) twice daily and as a reliever 2. Budesonide–formoterol (320/9 μg) twice daily and reliever SABA 3. Fluticasone–salmeterol (125/25 μg) twice daily and reliever SABA	Time to first severe exacerbation: SMART resulted in a longer time to first severe exacerbation than twice-daily budesonide–formoterol and reliever SABA ($P = 0.02$; log-rank test) or twice-daily fluticasone/salmeterol and reliever SABA ($P = 0.003$)	1. On the basis of time to first exacerbation, SMART therapy was superior to maintenance budesonide–formoterol and reliever SABA or fluticasone/salmeterol and reliever SABA. 2. SMART therapy resulted in a 28% reduction (rate ratio, 0.72; 95% CI, 0.57–0.90) and 39% (rate ratio, 0.61; 95% CI, 0.49–0.76) reduction in the rate of severe exacerbations compared with maintenance budesonide–formoterol with reliever SABA or fluticasone–salmeterol with reliever SABA.
PREPARE (NEJM 2021) (68, 69)	Open-label, pragmatic, multicenter, parallel-group RCT for 52 wk	18–75 yr old, self-identified as Black or Latinx, clinician-diagnosed asthma, prescribed ICS ± LABA, uncontrolled on the basis of ACT score	1,201	Usual clinical care with maintenance ICS ± LABA and reliever: 1. SABA, or 2. SABA + beclomethasone (80 μg) if using MDI or SABA + beclomethasone (400 μg) if using a nebulizer	Annualized rate of severe exacerbations: As-needed SABA + beclomethasone resulted in a decreased rate of severe exacerbations vs. SABA alone (0.82 vs. 0.69 severe exacerbations/yr; hazard ratio, 0.85; 95% CI, 0.72–1.00; $P = 0.048$)	In an open-label trial in Black and Latinx adults, on the severe exacerbation rate, the addition of an as-needed ICS to usual clinician care was superior to reliever SABA alone.

(*Continued*)

Table 2. (*Continued*)

Trial Name	Trial Design	Primary Inclusion Criteria	Participants (*n*)	Treatment Arms	Primary Outcome	Conclusion(s)
MANDALA (NEJM 2022) (70)	Double-blinded, multicenter, parallel-group RCT over 24 wk	⩾4 yr old with either a diagnosis of asthma and ⩾1 exacerbation in the prior yr, pre-BD FEV_1% 40–90% with ⩾12% reversibility, prescribed medium-to-high dose ICS ± LABA, uncontrolled on the basis of ACQ score	3,132	Usual clinical care with maintenance ICS ± LABA and reliever: 1. SABA (albuterol 180 μg) 2. Budesonide–albuterol (80/180 μg)* 3. Budesonide–albuterol (160/180 μg)	First event of severe exacerbation: Reliever use of high-dose budesonide–albuterol resulted in a decreased rate of severe exacerbations (hazard ratio, 0.74, 95% CI, 0.62–0.89) as compared with albuterol alone, but low-dose budesonide/albuterol did not (hazard ratio, 0.84; 95% CI, 0.71–1.00; $P = 0.052$)	Reliever budesonide–albuterol (160/180 μg) resulted in a lower rate of severe exacerbations than as-needed albuterol alone.

Definition of abbreviations: BD = bronchodilator; CI = confidence interval; COMPASS = effect of budesonide–formoterol maintenance and reliever therapy on asthma exacerbation; ICS = inhaled corticosteroid; LABA = long-acting β_2 agonist; MANDALA = as-needed albuterol/budesonide versus albuterol in adults and children aged at least 4 years with moderate-to-severe asthma; MDI = metered dose inhaler; OR = odds ratio; PREPARE = PeRson EmPowered Asthma Relief study; RCT = randomized controlled trial; SABA = short-acting β_2 agonist; SMART = Single Maintenance and Reliever Therapy; SMILE = effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomized controlled, double-blind study.
Throughout multiple randomized controlled trials, the reliever use of an ICS with formoterol or albuterol has shown superiority to similar maintenance therapy with reliever SABA therapy. The above represents only a small sample of these results and is not inclusive of all studies of a SMART approach. Systematic reviews and meta-analyses of SMART can be found by Cates and colleagues (142) and Sobieraj and colleagues (22). Notably, the PREPARE and MANDALA trials are not considered SMART but are shown to demonstrate data regarding the result of concomitant ICS and SABA reliever usage when prescribed with a separate maintenance inhaler.
*Only low-dose budesonide–albuterol was examined in children under 12 years old.

adoption of interventions (86). One classic example of this reality is the delayed adoption of β-blocker usage in heart failure management. Observations that β blockers improve mortality in heart failure were featured in prominent medical literature dating back to 1979 (87–90). Yet, the FDA did not approve the first β blocker for this indication, carvedilol, until 1997 (91). Moreover, the routine prescription of β blockers for heart failure was still below 40% in 2001 (92, 93). Undoubtedly, a missed opportunity for tangible public health benefits occurred during this 20-year evidence-to-practice gap. The field of implementation science was created to narrow these gaps. Recognizing its importance over the past 2 decades, implementation science has received ever-increasing attention from the NIH (National Institutes of Health) and professional societies, including the ATS (American Thoracic Society) (94, 95).

Implementation science attempts to understand the complex variables that cause an evidence-based intervention to be used, or frequently not used, in the real world. The evidence for implementation comes in multiple forms and is complex and dynamic (96). In collaboration with multiple stakeholders, implementation scientists elucidate facilitators and barriers to real-world adoption of evidence-based practices using implementation science frameworks, theories, and models (86). Implementation strategies are then developed to disseminate recommendations and implement evidence-based practices (97). Grounded in part in Diffusion Theory, implementation science is deliberate and proactive in contrast to the passive dissemination of scientific discoveries and guideline recommendations that theoretically follow a slow curvilinear diffusion process (Figure 4) (98).

Significant Real-world Barriers to the Adoption of New Inhaler Approaches Exist

Despite the potential for public health benefits, reliever usage of ICS–formoterol inhalers in asthma is infrequent in the United States, particularly in primary care and emergency department practice, which is

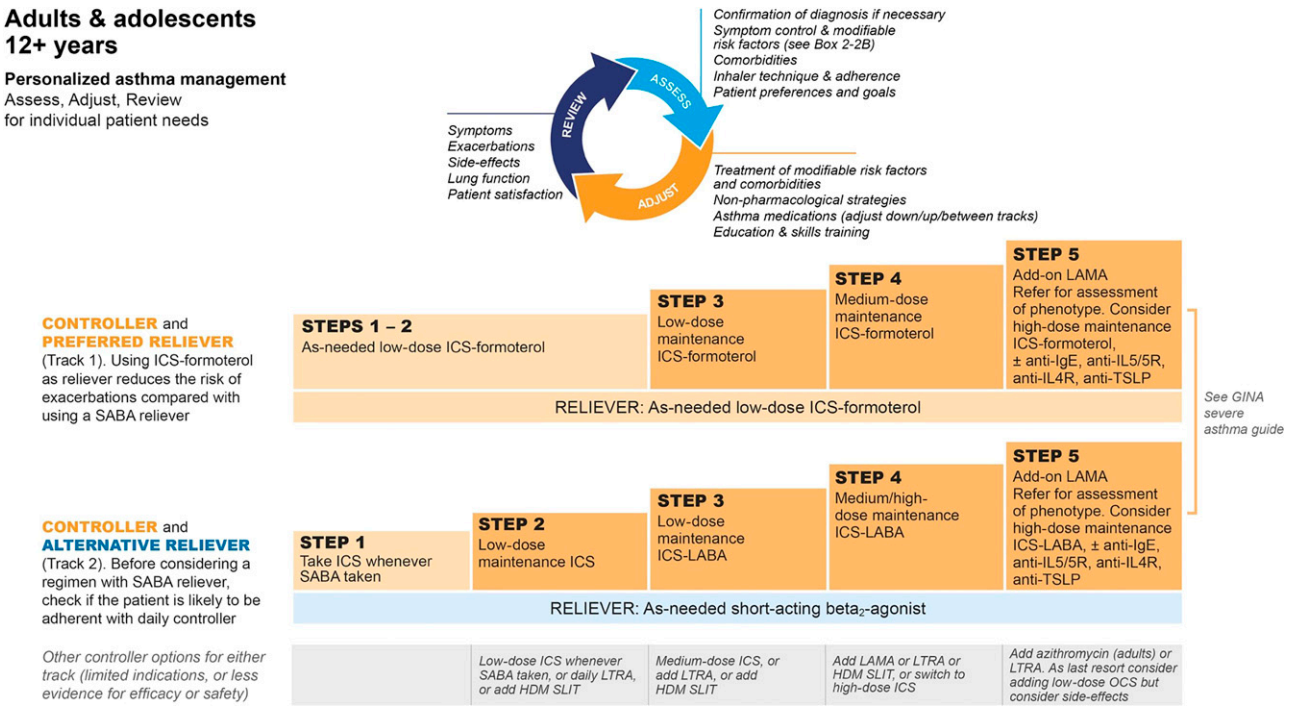

Figure 2. GINA (Global Initiative for Asthma) 2022 recommendations for the management of individuals at least 12 years old with asthma. GINA 2022, reprinted with permission. Available from www.ginasthma.org. HDM = house dust mite; ICS = inhaled corticosteroid; LABA = long-acting β_2 agonist; LAMA = long-acting muscarinic antagonist; LTRA = leukotriene receptor antagonist; OCS = oral corticosteroids; SABA = short-acting β_2 agonist; SLIT = sublingual immunotherapy; TSLP = thymic stromal lymphopoietin.

where most patients with asthma receive care (99). We postulate on the multiple barriers to the use of reliever ICS–formoterol inhalers and opportunities for implementation research in (Table 3) (59, 77, 80, 100).

Importantly, despite SMART being recommended by the U.S.-based NAEPP guidelines and approved by regulators in more than 120 countries, budesonide–formoterol inhalers are currently not FDA-labeled for reliever usage in the United States, which has cascading effects on prescription decisions (59, 101). Pharmaceutical formulary practices are a particular obstacle for SMART therapy (102). Prescription drug formularies outline the medications available to patients on the basis of their insurance plan; theoretically, formularies should also facilitate evidenced-based prescribing practices by selecting recommended medications for the lowest cost-sharing tier (103, 104). However, in the United States, formularies often consider all ICS–LABAs as interchangeable, and the choice of a preferred ICS–LABA frequently changes for a patient–insurance dyad (105). Consequently, if a clinical provider uses budesonide–formoterol in line with the latest evidence, the prescription may be substituted for another ICS–LABA combination that does not contain the quick-onset formoterol necessary for reliever usage. Furthermore, if a patient uses two puffs twice daily of budesonide–formoterol and the same inhaler on a reliever basis, they could run out of their 120-actuation inhaler before the end of the month when they are eligible for a refill.

These barriers, if not quickly addressed, delay the implementation of evidence-based practices in the United States. They also run counter to patient preferences. Patients with asthma have endorsed that the latest inhaler recommendations are more intuitive while also fostering a greater sense of self-efficacy (30, 106). Simply put, failure to think about implementation, promote facilitators, and address real-world barriers to the newest asthma recommendations will result in preventable asthma morbidity in the United States over the coming years.

A Bold Consideration to Expand ICS–Formoterol Access and Reduce Inhaler Cost: A Prescription (Rx)–to–Over-the-counter (OTC) Transition

As the asthma treatment paradigm shifts toward more widespread use of ICS–formoterol inhalers, ensuring that these inhalers are affordable and readily accessible will be critical to improving outcomes and asthma-related healthcare disparities. In the United States, changing budesonide–formoterol inhalers (e.g., budesonide–formoterol 160/4.5 μg MDI one puff for symptoms for adults/adolescents and 80/4.5 μg one puff for symptoms for children) from Rx-only access to OTC status (Rx-to-OTC) is one course of action that should be seriously considered and has the potential to decrease inhaler cost and decrease real-world usage of SABA monotherapy (107, 108). Although the pros and cons of an Rx-to-OTC transition for

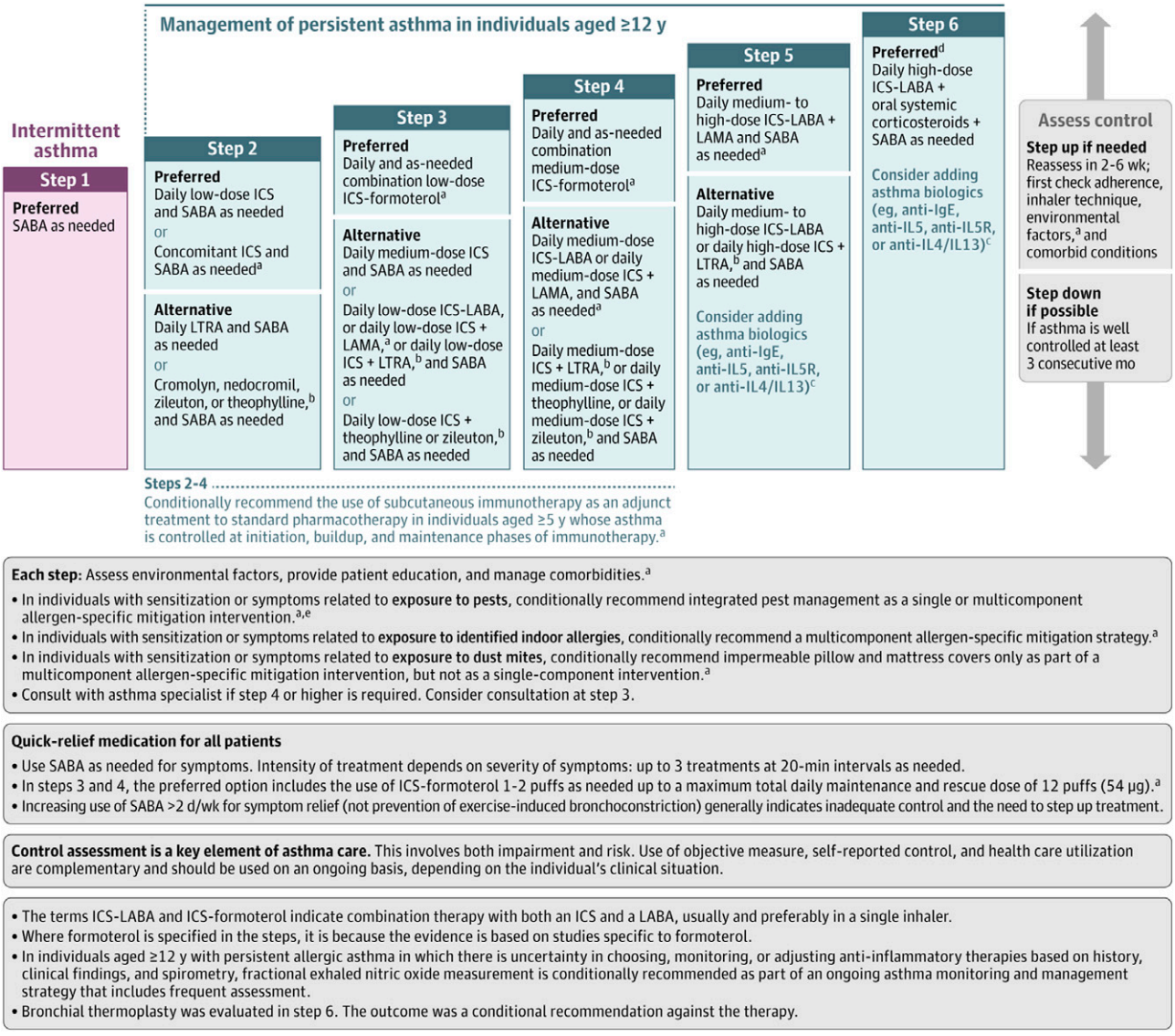

Figure 3. NAEPP (National Asthma Education and Prevention Program) 2020 recommendations for the management of individuals at least 12 years old with asthma. Note that the NAEPP did not address step one or step six management in their update published in 2020 because of prespecified objectives. [a]New recommendation on the basis of the 2020 Asthma Guideline Update. [b]Cromolyn, nedocromil, leukotriene receptor antagonists, inhibitors of 5-lipoxygenase (including zileuton and montelukast), and theophylline were not considered for the update. These have limited availability for use in the United States and/or have an increased risk of adverse consequences and need for monitoring that make their use less desirable. The U.S. Food and Drug Administration issued a boxed warning for montelukast in March 2020 because of adverse effects related to serious behavior- and mood-related changes. [c]The AHRQ (Agency for Healthcare Research and Quality) systematic reviews that informed the update did not include studies that examined the role of asthma biologics (anti-IgE, anti–IL-5, anti–IL-5R, and anti–IL-4/IL-13). Thus, this report does not contain specific recommendations for the use of biologics in asthma in steps five and six. [d]Data on the use of long-acting muscarinic antagonist therapy in individuals with severe persistent asthma (step six) were not included in the AHRQ systematic review; thus, no recommendations were made. [e]Pests refers to mice and cockroaches, which were specifically examined in the AHRQ systematic review. Figure reproduced with written permission from Cloutier and colleagues (83). ICS = inhaled corticosteroid; LABA = long-acting β_2 agonist; LAMA = long-acting muscarinic antagonist; LTRA = leukotriene receptor antagonist; SABA = short-acting β_2 agonist.

other inhalers could also be considered, we chose budesonide–formoterol as our exemplar because there are substantial clinical trial data supporting its safety and efficacy, which has led to it being the preferred reliever inhaler at all steps by GINA and two steps by NAEPP. Furthermore, budesonide–formoterol is now available as a generic option in the United States, and its use as an OTC medication would not lead to unopposed SABA use if used as a reliever. There is a substantial risk of any inhaler that contains a β agonist alone being available OTC because it facilitates real-world use of β-agonist monotherapy.

In the United States, the only currently approved OTC inhaler for asthma contains a β agonist alone (inhaled epinephrine;

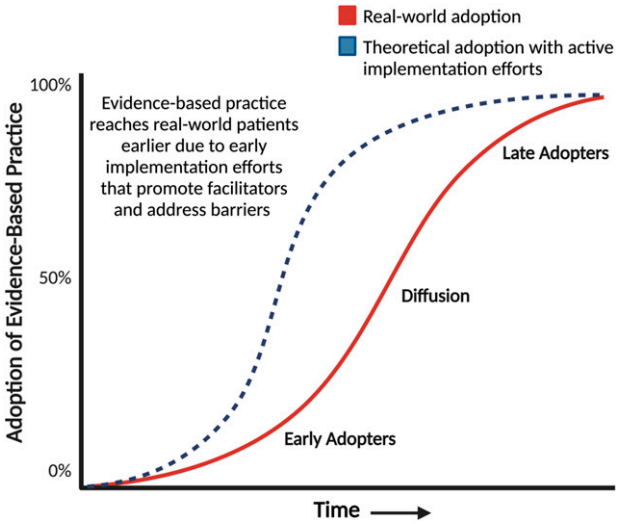

Figure 4. Theoretical curvilinear process of the diffusion of innovations. Innovations often spread following an S-shaped curvilinear process wherein a select few adopt an intervention early (early adopters). This is followed by slow diffusion that happens with word-of-mouth communication and positive experiences reinforcing this communication and, finally, adoption by late adopters. Active implementation attempts to understand what facilitators and barriers exist in the real world to shift and expedite the uptake of an evidence-based intervention (i.e., transition the adoption of a practice from the solid red line to the dotted blue line). Figure adapted from *Diffusion of Innovation* (98).

marketed as Primatene MIST). The recent reapproval of this epinephrine inhaler as an OTC device occurred despite concerns from the ATS and other health organizations (109). Proponents of this move noted that the OTC status of this inhaler made "access to [a] life-saving medication … affordable, convenient, and [provided] a safety net for medically marginalized and underinsured populations" (109). Given the association of uncoupled β-agonist use with increased mortality (particularly for those like epinephrine that have low β_2 selectivity) (110) and the greater safety and efficacy data surrounding reliever use of ICS–formoterol, continuing to provide aerosolized epinephrine as a safety net for patients with poor access to medications is arguably unethical (111, 112).

Why is inhaled epinephrine the only reliever medication available OTC in the United States, whereas superior inhalers are not available OTC? The answer is partially a historical accident because of inhaled epinephrine's marketing before modern FDA regulatory oversight (113). However, this unique designation is also likely attributable to pharmaceutical companies' financial self-interests (108). Amphastar Pharmaceuticals Inc. earned $73 million in net revenue from Primatene MIST sales in 2021 (114). This monetary reward may have driven Amphastar's persistent effort to obtain FDA approval to be the only OTC asthma inhaler despite the rejection of its original application in 2014 (109). As large as Amphastar's financial gains are, they are trivial compared with the potential financial losses other pharmaceutical companies could suffer if the billion-dollar market for current Rx-only inhalers were disrupted by an Rx-to-OTC switch (115).

Rx-to-OTC switches generally reduce drug prices, which would be critical if OTC placement of budesonide–formoterol were to improve medication access for patients with fewer financial resources (116). For example, the Rx-to-OTC switch of the second-generation antihistamine loratadine reduced its price by 99% in the early 2000s (117). Although currently stymied by legal processes, the FDA recently approved the first generic budesonide–formoterol inhaler (118–120). More generic budesonide–formoterol inhalers are likely to emerge, which may be hastened by OTC status and new competition (116). The current price of a budesonide–formoterol inhaler in the United States is $307 (121). The price of Primatene MIST is $29 (121, 122). Typically, branded medication prices fall 30% after the first generic competitor enters the market, 50% after the second, and 95% after the sixth (123). With adequate generic competition, it is not unreasonable to expect that the price of budesonide–formoterol could substantially decrease and make it a highly accessible OTC option in the future.

Neither the presence of a suboptimal alternative medication that has OTC labeling nor a desire to improve access to an evidence-based inhaler are sufficient reasons to advocate for a controversial Rx-to-OTC switch of budesonide–formoterol. Rx-to-OTC switches require careful and serious deliberation. Some studies have demonstrated that patients have the maximum symptom control, with a low exacerbation risk, when they maintain greater than 80% adherence to a maintenance ICS-containing regimen supplemented by infrequent reliever SABA use (124, 125). However, this ideal strategy depends on unrealistic assumptions about patient behavior. Decades of adherence research have demonstrated that high-maintenance inhaler adherence is not achievable in the real world except among a small group of highly motivated patients (126–129).

Another concern is that a potential Rx-to-OTC switch for a new inhaler would lead to patients' inappropriate self-diagnoses and harmful self-management. However, provider control over inhaler prescriptions has not prevented over 25% of patients from using amounts of SABA associated with mortality (38). When prescribed a maintenance inhaler and SABA, patients can easily choose which Rx to fill, and clinicians cannot prevent patients from preferentially filling their SABA Rx. For this reason, prescribing separate maintenance and SABA reliever therapy is often illusory. If forward-thinking action were taken, making budesonide–formoterol inhalers the only OTC option in the United States, then theoretically, patients' ICS exposure would increase, whereas SABA monotherapy use would decrease. An Rx-to-OTC switch of budesonide–formoterol is not a solution that would cure all issues. The point of this proposal is simply that an OTC ICS–formoterol inhaler is much safer than the current OTC option, may go a long way to improve overreliance on SABAs alone, may drive down inhaler cost, and would provide a more acceptable safety net for patients, which makes it worthy of serious consideration.

Table 3. Potential Real-world Barriers to the Implementation of Reliever Inhaled Corticosteroid–Formoterol Usage in the United States and Need for Future Research and Action

Potential Barrier to Implementation of Reliever ICS–Formoterol Inhalers in the United States	Explanation of Potential Barriers and Knowledge Gaps	Future Work Needed
Provider knowledge	• At least 60% of chronic asthma care occurs in primary care settings. • Specialist and primary care clinician knowledge of the logistics of a reliever-only ICS-formoterol approach and SMART is largely unknown.	• Better understanding of successful knowledge dissemination strategies in primary care and specialty settings.
Discordance between guidelines	• Important differences exist between the GINA and NAEPP recommendations. • The role this discordance plays in a provider's decision to use ICS–formoterol inhalers on a reliever-only basis is unclear.	• Dissemination of GINA and NAEPP recommendations. • Expeditious update to NAEPP 2020 update that includes management recommendations at steps one and six. • Consider a more dynamic way to continuously update guidelines, given the increasing rate that evidence emerges.
Medico–legal and regulatory issues	• Clinical trials of new inhaler approach are primarily on the basis of dry-powder budesonide–formoterol (not available in the United States). • FDA-labeling of budesonide–formoterol does not include its use as a reliever inhaler.	• Explore the extent to which these factors influence clinician decision-making. • Encourage FDA approval of budesonide–formoterol for reliever use.
Pharmaceutical coverage concerns and cost	• Pharmacy benefits and formulary practices may preferentially cover ICS–LABA inhalers that do not include formoterol and cannot be used as a reliever device and with SMART. • Annual formulary changes may promote the substitution of formoterol-containing ICS–LABAs for non–formoterol-containing combinations.	• Comparative cost-effectiveness analyses of reliever ICS–formoterol therapy and SMART therapy as compared with traditional management. • Advocate for classifying rapid-onset and non–rapid-onset LABAs into separate pharmacological categories.
Patient preference for reliever nebulizers*	• Real-world usage of nebulizers for symptom relief is common in asthma. In patients who prefer nebulizers, instructions on how to or if we should use new inhaler approaches are not clear.	• Clarify what recommendations should be made to patients who prefer nebulizers when using the latest asthma recommendations/guidelines.
Integration into asthma action plans	• The use of asthma action plans is recommended. Historically, asthma action plans have not incorporated reliever ICS–formoterol usage or SMART.	• Develop, test, and disseminate model asthma action plans that use reliever-only ICS–formoterol and SMART.
Lack of incentives to move toward SMART	• Health systems and payers may not recognize the opportunity to reduce rates of severe asthma exacerbations with SMART.	• Study the effects of health plan or health system interventions to promote the uptake of SMART. • Examine the effects of SMART usage on preventable emergency care, hospitalization, and costs of asthma care on a system level.

Definition of abbreviations: FDA = U.S. Food and Drug Administration; GINA = Global Initiative for Asthma; ICS = inhaled corticosteroid; LABA = long-acting β_2 agonist; NAEPP = National Asthma Education and Prevention Program; SMART = Single Maintenance and Reliever Therapy.
*We do not promote nebulizer usage of reliever asthma medications over inhaler usage as some studies have shown that nebulizers are associated with a higher risk of asthma morbidity (143). However, we do recognize that many real-world patients prefer nebulizers (68, 144). As such, in patients who clearly prefer nebulizer usage and in whom a provider is considering SMART or reliever-only ICS–formoterol therapy, optimal patient instructions should be explored and clarified.

A Call to Action

We believe it is time to rethink how the typical patient with asthma is managed in the United States. Expediting the real-world adoption of reliever ICS–formoterol inhalers (either as a reliever-only option in mild asthma or as part of SMART) should be prioritized. Using proven implementation science methodologies, researchers should engage patients, clinicians, pharmacists, insurance companies, policymakers, and other stakeholders to discern the real-world facilitators and barriers to using reliever-only ICS–formoterol regimens and SMART.

For example, templates for asthma action plans should be updated with critical feedback from clinicians and patients. This work has already been done in some countries but needs to be adapted for the United States and other locations (59). In addition, the FDA should relabel budesonide–formoterol as both a maintenance and reliever therapy in the United States now. This action would bring the U.S. labeling of budesonide–formoterol in line with more than 120 other countries and be concordant with recommendations from both GINA and the NIH-sponsored NAEPP guidelines.

The most obvious route for seeking new budesonide–formoterol labeling (as a reliever and for OTC dispensing) is by the initiation of the process from the drug manufacturers; however, if this is not in their financial interests, then other sponsors (e.g., third-party payers, patient advocacy organizations, or professional organizations such as ATS) could request labeling changes (130, 131). Furthermore, although rarely attempted, the FDA could force a switch through its regulatory powers. There are, of course, both benefits and risks to extrapolating data on the efficacy of dry-powder ICS–formoterol formulations to U.S.-specific formulations. If regulators believe more studies are needed with U.S.-specific ICS–formoterol devices before relabeling, then those studies should be organized and completed expeditiously. As it stands, our collective delay in relabeling ICS–formoterol inhalers as both a maintenance and reliever device is likely depriving patients of greater access to an evidence-based inhaler approach that would benefit many.

There is accumulating data on the use of a combination ICS–SABA as a reliever, but this should not delay the needed action on budesonide–formoterol. The recent MANDALA (as-needed albuterol/budesonide vs. albuterol in adults and children aged at least 4 years with moderate-to-severe asthma) trial demonstrated benefits of reliever budesonide–albuterol in moderate-to-severe asthma (31), and PREPARE (PeRson EmPowered Asthma Relief) showed the benefits of providing separate ICS for use whenever SABA is taken (68, 69). In November 2022, the FDA Pulmonary–Allergy Drugs Advisory Committee recommended approval of budesonide–albuterol for as-needed treatment or prevention of bronchoconstriction in adults but not for adolescents or children (132). Both the potential lack of FDA labeling for budesonide–albuterol as a reliever in adolescents and children, as well as the paucity of data on reliever-only budesonide–formoterol therapy and SMART in children under 12 years, should prompt pediatric-specific trials in these areas.

Although a potential combination ICS–SABA reliever is preferential to a SABA-only reliever, differences between budesonide–formoterol and budesonide–albuterol should be noted. First, in mild asthma, data for the use of reliever ICS–SABA therapy while not part of a strategy with a maintenance therapy is sparse, with only 235 adults and 174 children/adolescents having been randomized to this therapy to date (27–30, 133). Moreover, importantly, in moderate-to-severe persistent asthma, SMART (wherein the same inhaler can be used conveniently as both a maintenance and reliever device) is only currently possible with an ICS–formoterol device.

To stimulate this work, the ATS should play an active role, including the formation of a working group to tackle these proposals. We also believe an update to the NAEPP 2020 guidelines is urgently needed because of the emergence of significant new data since its last iteration (84). The most recent NAEPP guidelines are on the basis of studies published through October 2018, and do not include the four paradigm-shifting studies of reliever-only ICS–formoterol conducted in almost 10,000 adults and adolescents with mild asthma (23–26).

As we consider future work, we should acknowledge that there are significant healthcare disparities in asthma, and inhaler costs are too high (111). If we do not explicitly integrate a health equity lens into our upcoming efforts, we should expect our latest evidence-based inhaler approaches to reach patients from higher socioeconomic statuses first, whereas lower-income patients continue to use suboptimal inhaler paradigms. Prescription of biological therapeutics in asthma is already revealing uneven access, with providers more likely to prescribe these medications to higher-income White patients (134, 135). Frameworks for implementation efforts that explicitly consider equity outcomes exist and have been used in other fields (136–139).

Finally, all strategies to increase inhaler access while driving down cost, however bold, should be on the table. Changing ICS–formoterol inhalers to OTC should be treated as a serious option. At present, the official ATS position opposes making prescription-only inhalers, particularly SABAs, available OTC. Providing OTC options for inhalers was seriously considered by the FDA back in 2012 (140). However, a lot has changed since the last time the ATS and FDA considered an Rx-to-OTC change for inhalers. Today, a suboptimal epinephrine inhaler is available OTC, ICS-containing inhaler costs remain unrelentingly high, and new data has emerged on an efficacious reliever ICS–formoterol option. These facts should prompt a re-examination of the advantages and disadvantages of an Rx-to-OTC change for ICS–formoterol inhalers.

Conclusions

A new paradigm for treating patients with asthma is emerging wherein combination ICS–formoterol inhalers are simpler, more effective, and a safer alternative to SABA inhalers for reliever therapy. For the public to benefit from new inhaler approaches, it will be necessary to ensure these new approaches are accessible and affordable. We believe now is the time to take the next steps toward implementation while learning why clinicians are, or are not, following the latest asthma recommendations. One bold option to consider is transitioning budesonide–formoterol to OTC status. Powerful opposition to these proposed changes is likely to be encountered because of deontological imperatives within the medical profession as well as financial self-interests in the U.S. health system. Nonetheless, we currently have an opportunity to radically change how we treat asthma and reduce some of the preventable burdens our patients face. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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