Over-the-counter Dispensing: Widening Access to Inhaled Corticosteroid/Formoterol Reliever Therapy

The limited availability of low-dose inhaled corticosteroid (ICS)/formoterol reliever therapy in many countries is an issue of international concern. As recommended by the GINA (Global Initiative for Asthma) strategy, ICS/formoterol is preferred to short-acting β_2 agonists (SABA) as reliever therapy in adolescents and adults with asthma across the range of asthma severity (1, 2). As-needed ICS/formoterol reduces the risk of severe exacerbations by between 55% and 32% compared with SABA reliever therapy when taken alone in mild asthma (3) or together with maintenance ICS/long-acting β_2-agonist (LABA) therapy in moderate or severe asthma, respectively (4). It reduces the risk of β_2 agonist overuse in the situation of worsening asthma and the associated delay in seeking medical review, both key risk factors for asthma mortality (5). It allows titration of ICS use according to changes in asthma severity through the vehicle of bronchodilator use and ensures delivery of ICS therapy in patients not prescribed or nonadherent to maintenance ICS-based medication. It is simple to use, requiring only one inhaler device regardless of severity and is the regimen preferred by most patients (6).

However, as discussed in an authoritative review in this issue of the *Journal*, Krings and colleagues (pp. 390–405) note numerous barriers to implementing this approach in real-world practice, particularly in the United States (7). As the authors outline, despite the evidence above and the ICS/formoterol SMART (Single Maintenance And Reliever Therapy) regimen being recommended by the U.S.-based NAEPP (National Asthma Education and Prevention Program) guidelines (as well as by GINA) and approved by regulators in more than 120 countries, budesonide/formoterol (the specific ICS/formoterol product for which almost all the evidence of benefit and safety exists) is not currently approved by the U.S. Food and Drug Administration for reliever use.

The authors make a number of recommendations to overcome the inevitable downstream effects of this lack of regulatory approval, including the paradigm shift to make budesonide/formoterol available as an over-the-counter (OTC) medication. A strong case is made that this regulatory action would have the potential to markedly improve the availability of budesonide/formoterol, particularly for disadvantaged populations, and thereby lead to better outcomes in asthma and reduce the burden of disease, enhance patient safety, reduce the mortality risk with SABA monotherapy, and substantially reduce inhaler and healthcare costs. Importantly, in the United States, such an action would provide a much-needed safer and more effective choice to the current OTC availability of aerosolized epinephrine, an α and β agonist, for which there is only low-quality evidence that it has similar efficacy as a β_2-selective agonist (8). ICS/formoterol reliever alone would overcome the real concerns with the use of epinephrine taken without concomitant ICS therapy, ensuring that all patients received an ICS at the same time that their reliever was administered, titrating the dose of ICS according to changes in asthma severity.

Although the case in favor of OTC budesonide/formoterol is convincingly made, are there any outstanding issues that inform these considerations? The first relates to the use of ICS/formoterol as a reliever alone: how does it compare with other treatment regimens recommended for mild or moderate asthma, although presumably not available to patients accessing OTC medication? In a network meta-analysis of clinical trials in adolescents and adults with asthma, ICS/formoterol reliever alone was ranked higher than low-dose maintenance ICS/LABA plus SABA reliever or low- or medium-dose maintenance ICS plus SABA reliever in terms of exacerbation risk reduction (9). SABA reliever therapy alone ranked the lowest of the 10 inhaled therapeutic regimens included in the analysis.

The second issue relates to the use of ICS/formoterol according to the SMART regimen: how does it compare with other treatment regimens recommended for moderate or severe asthma, likewise not otherwise available to patients seeking OTC medications? The network analysis reported that low- and medium-dose ICS/formoterol, according to the SMART regimen, ranked higher than all 8 other inhaled therapeutic regimens, including low-, medium- and high-dose ICS/LABA maintenance plus SABA reliever therapy (9).

Although these data are reassuring, the issue of safety with repeated use in the situation of a severe attack of asthma also needs consideration. The recent randomized controlled trial of cumulative high doses of albuterol and budesonide/formoterol, as would be used in the treatment of a severe attack resulting in hospital admission, is informative (10). There were significantly more adverse events during the albuterol regimen compared with budesonide/formoterol when administered repeatedly in the ratio of 200 μg versus 200/6 μg, respectively, with 5% of participants withdrawn because of safety concerns after albuterol use. At 180 minutes, albuterol resulted in a 0.26 mmol/L greater reduction in serum potassium and a 10 beats/min greater heart rate, indicating greater systemic β_2 and β_1/β_2 effects, respectively. The acute increase in FEV_1 was greater with albuterol initially, without a difference in perception of breathlessness, and budesonide/formoterol achieved a greater FEV_1 later in the time course.

Although the clinical relevance of differences in bronchodilator efficacy in the community setting is a moot point, as the patient can simply take an additional dose if needed to relieve symptoms, the lesser β_1- and β_2-agonist systemic adverse effects of ICS/formoterol compared with albuterol, when given in these comparative doses, is likely of clinical relevance. Furthermore, as asthma mortality epidemics have been associated with high-dose preparations of poorly selective β_2 agonists, the relatively lower

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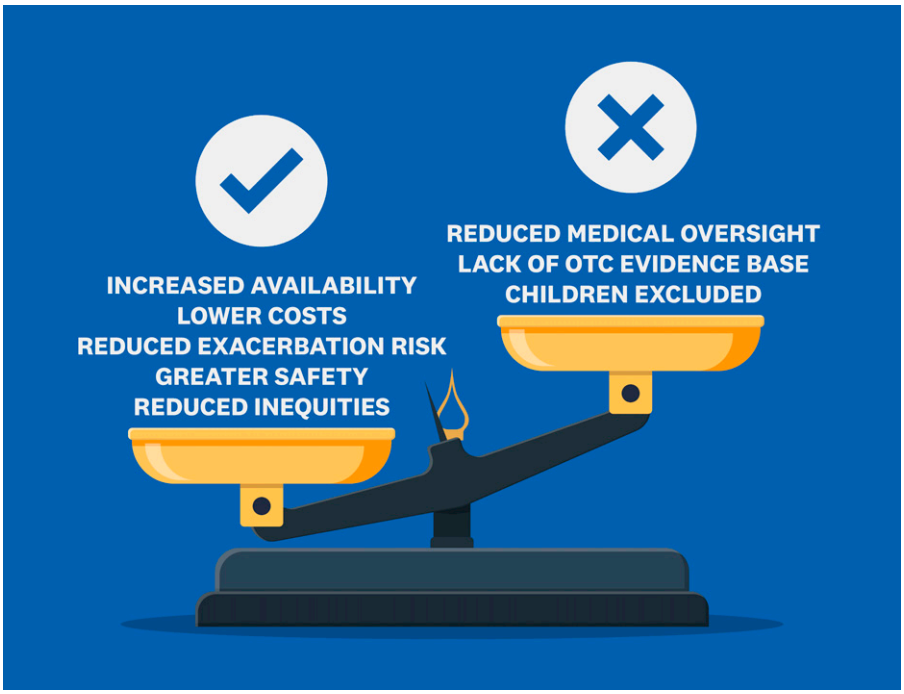

Figure 1. Over-the-counter dispensing of inhaled corticosteroid/formoterol: balancing the pros and cons. OTC = over-the-counter.

β_2-agonist dose of ICS/formoterol may have a potential safety advantage when compared with albuterol, and the greater β_2-agonist selectivity a potential safety advantage compared with epinephrine. The observation that as-needed ICS/formoterol reduces the risk of asthma-related hospital admission or emergency department or urgent care visit by 65% compared with as-needed albuterol is consistent with potentially reduced mortality risk (4, 11).

Finally, despite the above evidence demonstrating the efficacy and safety of ICS/formoterol reliever therapy in adults and adolescents, there is a worrying lack of evidence in children under 12 years of age to support its prescribed, let alone OTC, use. Randomized controlled trials in this age group across the spectrum of asthma severity are an urgent priority.

In summary, the review makes a persuasive case for attention to move from the evidence base for the efficacy/safety profile of ICS/formoterol reliever therapy in asthma to measures needed to ensure affordable access to this regimen. Although this may require different initiatives in different healthcare systems, OTC availability for adolescents and adults with asthma should be seriously considered. It is not a matter of whether there are no risks with this approach but rather whether the potential benefits outweigh the potential risks (Figure 1). We propose that this is the case but submit that it would be crucial for the outcome of such a regulatory action to be closely assessed in different jurisdictions to guide its implementation more widely. ■

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Evolution of Lung Function within Individuals: Clinical Insights and Data-driven Methods

Spirometric impairments at the physiological peak in early adulthood are associated with adverse health outcomes through the life course (1), including poor respiratory health and a higher risk of chronic obstructive pulmonary disease (2), but also cardiovascular and cerebrovascular events into middle age (3). Among children with asthma, reduced lung function predicts the persistence of severe disease to adulthood (4). These studies identified diminished lung growth in childhood as an important indicator of poor health in adulthood and highlighted the importance of interventions to preserve/improve lung function during childhood to prevent the onset and progression of ill health. However, it remains unanswered how best to identify individuals at risk and which preventive measures to apply.

In recent years, a substantial effort has been devoted to identifying lifetime trajectories of different spirometric measures of lung function and their predictors using data-driven methods (5–10). These models can quickly process large amounts of data and identify patterns humans cannot easily observe. Because of the limited availability of repeated spirometry in children, relatively few studies applied analytical modeling to childhood lung function (5–7). Two multicohort studies reported age-specific prevalence of spirometric impairments from childhood to peak in early adulthood, with airway obstruction ranging from 3% to 11% and restrictive pattern from 2% to 8% (11, 12). Longitudinal models identified between two (6) and four (5, 7) distinct trajectories extending from school age into adolescence/early adulthood, characterized by apparently stable lung function through childhood, depicted by parallel lines. These findings are usually interpreted as lung function tracking through childhood. Of note, these data-driven analyses revealed no evidence of latent classes/clusters of children with declining (or improving) lung function. In contrast, clinical experience and visualization of within-individual trajectories suggest considerable variability between children, with lung function improving in some and declining in others. Furthermore, one previous study, which modeled childhood lung function trajectories using repeated measures of specific airway resistance rather than spirometry, reported that children with persistent wheeze, frequent exacerbations, and early atopy are at risk of a decline in lung function between ages 3 and 11 years and that these effects are more marked in boys (13). Modeling of spirometry data extending to later adulthood (45–55 yr) described six trajectories, four of which were strikingly similar to childhood trajectories (8). One additional trajectory was characterized by an accelerated decline in later adulthood and another by early low lung function but with accelerated growth (8).

So, why are clusters of children with declining and improving spirometry not readily identified using data-driven methodologies? Is spirometry too blunt a tool to detect subtle but potentially important temporal trends (13), or is the follow-up to early adulthood too short (8), or is the proportion of decliners and improvers through childhood too small to be detected in relatively small sample sizes with repeated spirometry available in birth cohorts? And why would it be important? We would argue that understanding the associates of lung function decline and improvement through childhood is of key importance to developing actionable interventions to improve lung function growth.

In this issue of the *Journal*, Wang and colleagues (pp. 406–415) report the analysis of lung function development from childhood to early adulthood in two unselected birth cohorts, which used a data-driven Markovian dependent mixture model to identify five lung function states (very low, low, normal, high, and very high) at three cross-sectional points through childhood (14). The model used in this study, like many others, is a simplification of reality, but a more complicated model must be balanced against interpretability. Further frequentist analyses suggested that some participants in the low lung function states had catch-up to normal but that growth failure occurred in some participants with initial normal/high lung function. Longitudinal lung function through childhood to early adulthood and meticulous follow-up of study participants are some of the strengths of the study. However, there are unavoidable weaknesses.

Although lung function states were derived using data-driven methods, the definition of catch-up and growth failure trajectories

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