

It is Time to Change How We Manage Mild Asthma

Written by Dr Aoife O'Reilly & Professor Eleanor Dunican, St. Vincent's University Hospital and University College Dublin

Management of asthma has traditionally relied on inhaled corticosteroid (ICS) used regularly for asthma control as well as inhaled short-acting beta agonist (SABA) used as needed for symptom relief. In 2019, the Global Initiative for Asthma (GINA) made a fundamental change to its recommendations for the treatment of asthma. GINA no longer recommends regular use of SABA as a reliever without an ICS. All patients diagnosed with asthma should be prescribed an ICS, either regularly or as needed for respiratory symptoms. In patients with mild asthma, ICS/formoterol should be used as a reliever instead of regular ICS, to avoid the risk of patients reverting to SABA monotherapy. This article outlines the rationale and evidence that supports the most radical change to asthma management in the last 50 years.

The history of SABAs indicated a problem early in their use

SABAs were the first inhaled therapy commonly prescribed for asthma and provide symptomatic relief (within 5 minutes) through rapid-onset bronchodilation but have no anti-inflammatory properties. Therefore, with the sudden rise in SABA use in the late 1950s, there was a calamitous rise in asthma deaths in England and Wales, with an almost 400% increase in deaths from asthma in the 5-34 year age group. This sudden epidemic of asthma deaths was thoroughly investigated, and many theories were proposed to explain it. SABA toxicity was thought to be the most likely explanation. Less traction was given to the alternative theory that over-reliance on the reliever effects of SABAs led to fatal delays in patients seeking medical care. Subsequently, after a warning was issued that excessive use of SABAs was dangerous, the sales of SABAs dropped precipitously and asthma deaths returned to pre-pandemic levels. Authorities concluded that high doses of SABAs are toxic and the direct cause of rise in asthma deaths seen with their introduction. Incidentally, the same year the warning was issued, admissions to hospital for asthma and prescriptions for systemic

corticosteroids increased, both important management steps in treating life-threatening asthma attacks. Since then, many studies over the decades have replicated a dose-dependent association between overuse of SABA and asthma mortality.

Pharmacological management of mild asthma relied on SABA monotherapy

ICSs were introduced into clinical practice in the early 1970's and revolutionised the management of asthma. ICSs reduce airway inflammation and airway hyperresponsiveness, improve asthma control and reduce exacerbations, making them the cornerstone of asthma management.

ICS and SABA are the most commonly prescribed therapies for asthma, but the way in which they have been traditionally prescribed to those with mild to moderate asthma does not align to the underlying biology of the disease. Before 2019, guidelines internationally recommended SABA monotherapy as first line treatment for mild asthma (symptoms less than twice a month), even though many studies have shown inflammatory airway changes present across the entire spectrum of asthma severity. The rationale for this recommendation was the belief that prescribing regular ICS to patients with infrequent symptoms would be excessive and poorly adhered to. From a patient's perspective, the most tangible measure of asthma control is day-to-day symptoms. Patients with mild asthma often fail to notice any obvious difference in symptoms while taking regular ICS, but notice rapid improvement with SABA, leading to the belief that the SABAs are more effective at controlling their disease.

ICS with SABA for symptom relief is superior to regular ICS in mild asthma

Studies have shown that use of regular ICS is superior to as-needed SABA in reducing exacerbation risk in patients with mild asthma, and this benefit persists even when symptoms are very infrequent. To overcome the challenge of convincing



Dr Aoife O'Reilly,
St. Vincent's University Hospital
and University College Dublin



Professor Eleanor Dunican,
St. Vincent's University Hospital
and University College Dublin

relatively asymptomatic patients to take regular low-dose ICS, one potential approach was investigated: matching ICS inhaler use on a puff-per-puff basis with as-needed SABA. Studies in adult and paediatric populations have shown no difference in time to asthma worsening with symptom-driven use of ICS with SABA compared to regular ICS. However, this approach requires the patients to carry two inhalers for relatively infrequent symptoms, which may be challenging to achieve.

A study using a single combination inhaler containing ICS and SABA demonstrated that symptom-driven use of beclomethasone (ICS) and albuterol (SABA) in a single inhaler was as effective as regular use of beclomethasone and was associated with a lower 6-month cumulative dose of inhaled corticosteroid.

Symptom-driven ICS/formoterol use reduces exacerbations in mild asthma

However, since there are no combination ICS/SABA inhalers on the market, investigators have also studied symptom-driven use of formoterol, a long acting beta agonist (LABA) and budesonide (ICS) in a single inhaler. The choice of formoterol over other LABAs is due to its rapid onset (approximately 2-3 minutes) of action, making it suitable as a reliever. In mild asthma, symptom-driven use of formoterol/

budesonide was shown to be superior to SABA at preventing asthma exacerbations, and was more effective than regular low dose ICS (with as needed SABA) at preventing severe asthma exacerbations in mild to moderate asthma. ICS/LABA used as needed resulted in a 64% reduction in severe exacerbations and a prolonged time to first severe exacerbation compared to SABA.

Interestingly, the reduction in exacerbations seen with as-needed ICS/LABA is not driven by the anti-inflammatory ICS component alone. In patients using ICS regularly, as-needed LABA is superior to SABA at reducing exacerbations. However, as-needed use of ICS/LABA is superior to LABA or SABA alone.

Conclusion

Even patients with infrequent asthma symptoms can suffer severe or fatal asthma attacks. Overuse of SABA is associated with increased asthma mortality due to its lack of anti-inflammatory properties and resultant delay in patients seeking medical care. In patients with asthma symptoms less than twice a month, current recommendations are that they should be prescribed as-needed low-dose ICS-formoterol for symptom relief (preferred), or take low dose ICS whenever SABA is needed for symptom relief.