

## Safety of long-acting $\beta_2$ -agonists in the management of asthma

*A Primary Care Respiratory Alliance of Canada perspective*

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The controversy around the safety of long-acting  $\beta_2$ -agonists (LABAs) was revisited by the US Food and Drug Administration (FDA) at a meeting held on December 11, 2008.<sup>1</sup> Long-acting  $\beta_2$ -agonists have a duration of action of approximately 12 hours, considerably longer than short-acting  $\beta_2$ -agonists like salbutamol and terbutaline, which have a duration of action of about 4 hours. In Canada, the LABAs available include salmeterol, formoterol fumarate, and formoterol fumarate dihydrate. At the FDA meeting, a US advisory panel ruled that the 2 available LABA and inhaled corticosteroid (ICS) combination therapies (ie, fluticasone propionate plus salmeterol and budesonide plus formoterol fumarate dihydrate) were safe enough for treating asthma; but asthma-related deaths and serious complications led the expert panel to warn against continued use of salmeterol and formoterol fumarate as monotherapy for adults, adolescents, and children with asthma.

Both LABAs as monotherapy and LABAs in combination with ICSs have been linked by the FDA to adverse outcomes. Recent reviews<sup>2-6</sup> on the safety of LABAs in asthma management continue to raise important questions among caregivers. The ongoing debate might confuse some clinicians and patients and interfere with the medical management of this very common respiratory condition. As the use of LABA monotherapy is not contraindicated in patients with chronic obstructive pulmonary disease, distinguishing between asthma and chronic obstructive pulmonary disease represents an important undertaking for family physicians.

### Combination therapy

While the number of asthma deaths suspected of being related to LABA use is small, one hopes that a better understanding of LABA use will serve to improve overall asthma control. The possibility that LABAs might have harmful effects in patients with asthma has been suggested by 2 large clinical trials<sup>7,8</sup> and a recent meta-analysis,<sup>9</sup> which was heavily influenced by a single trial.<sup>8</sup> What is important for family physicians to consider is

that the trials reporting increased mortality and hospitalization with the use of LABAs included an alarming number of patients who were not taking ICSs. In a large Canadian study,<sup>10</sup> salmeterol did not increase serious exacerbations compared with placebo among patients with asthma using ICSs regularly. Although LABAs are extremely effective in improving symptoms and lung function, they do not appear to exert any meaningful clinically relevant anti-inflammatory effects. There are no recently published guidelines that recommend LABA use without concomitant ICS use.<sup>11,12</sup> It is very important to emphasize that routine use of LABA monotherapy in asthma should not be considered. Long-acting  $\beta_2$ -agonists should preferably be prescribed as LABA-ICS combination inhalers.

To date there are no studies large enough to definitively exclude an increased mortality risk with LABA use in individuals with asthma, even in those patients using ICSs. Therefore, family physicians must consider this potential risk at the population level when developing individual treatment strategies. As LABA use against a background of an inadequate ICS dose might seriously compromise asthma control and lead to death in some patients,<sup>8</sup> an important task for family physicians involves selection of appropriate ICS therapy before the addition of LABA therapy—recognizing that in the long-term, airway inflammation might vary and prompt a change in ICS dose in some individuals.

The theoretical possibility that airway inflammation can be masked does exist, and physicians should be aware of these implications.<sup>13</sup> A family physician confronted with a patient using only LABA therapy for asthma control should advise the patient of the potential life-threatening risks of this approach. The physician should discontinue the LABA and initiate a course of ICS therapy if asthma control appears suboptimal, including the use of a short-acting  $\beta_2$ -agonist for rescue therapy; formoterol has the additional benefit of rapid onset of action as well as being long-acting, which is not the case for salmeterol.<sup>14</sup> The addition of LABAs should be as combination inhalers, containing both LABAs and ICSs.<sup>6</sup> If the LABA-ICS combination does not result in acceptable asthma control despite adequate

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inhaler technique and environmental control strategies, a referral for specialty care should be considered.<sup>15</sup>

Two large, long-term landmark trials, FACET<sup>16</sup> (Formoterol and Corticosteroids Establishing Therapy) and GOAL<sup>17</sup> (Gaining Optimal Asthma Control), have provided evidence that fixed-dose LABA-ICS combination therapy greatly reduces the future risk of exacerbations and increases the time with improved asthma control compared with ICS therapy alone. The use of a single-inhaler combination (budesonide plus formoterol fumarate dihydrate) for both maintenance and rescue also appears to be safe and effective in asthma management.<sup>14</sup>

### Conclusion

More studies are required to better understand which asthma patients might be at increased risk of death as a result of pharmacotherapeutic interventions. As family physicians involved in the day-to-day care of patients with asthma, we might be well served to recognize that many end points should be considered when evaluating asthma control, acknowledging that some end points will be influenced more by bronchodilator medications and some more by ICS medications. Inhaled corticosteroids should remain first-line therapy for patients with persistent symptoms; LABAs should be added if symptoms are not adequately controlled on low-to-moderate ICS doses. With time, direct measurement of airway inflammation might become more commonplace in primary care. This information might allow us to more fully exploit the proven benefits of LABA-ICS combination therapy in asthma management. 

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### Competing interests

**Dr D'Urzo** has participated in many clinical trials studying the use of long-acting  $\beta_2$ -agonists and inhaled corticosteroids in asthma management that were funded by various pharmaceutical organizations.

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