Editorials

LABA monotherapy in asthma:

an avoidable problem

AN AVOIDABLE PROBLEM

Long-acting beta 2-agonists (LABAs) (or beta-adrenoceptor agonists) improve lung function and quality of life, and are recommended at step 3 of the national guidelines for the management of asthma.[1] However, chronic exposure to LABAs can be associated with tolerance and reduced sensitivity to the bronchodilator effects of salbutamol raising concerns over their use in asthma.[2] In 2006 a large randomised trial called SMART (Salmeterol Multi-Centre Asthma Research Trial) involving 26 355 patients randomised to either inhaled salmeterol or placebo in addition to their usual care was reported.[3] This trial found that significantly more serious adverse events and asthma-related deaths occurred in the salmeterol group. This risk was potentially confined to patients treated with LABA monotherapy only, as regular use of inhaled corticosteroids (ICS) was limited. A review of available data by the Medicines and Healthcare products Regulatory Agency (MHRA) concluded that the benefits of LABA/ICS combination therapy outweigh any potential risks in asthma.[4] For this reason, LABAs are currently recommended for the management of asthma in combination with an ICS only. In 2009 the British Thoracic Society/Scottish Intercollegiate Guideline Network (BTS/SIGN) national asthma guidelines recommended prescribing LABAs either as separate inhalers or in combination inhalers with ICS.[5] However, in 2011 BTS/SIGN revised their guidelines recommending that LABAs only be prescribed with ICS in combination inhalers (such as in a single device).[1] This revision was made because prescribing LABAs with ICS in combination inhalers is the only way of guaranteeing that LABA monotherapy and therefore the risks associated with LABA monotherapy do not occur.

LABA MONOTHERAPY IN PRIMARY CARE

UK primary care data has now been used to measure how often LABA monotherapy occurred among patients with asthma prescribed LABAs. This study showed that over the course of a year just under one-third of people with asthma were prescribed a LABA, and one-quarter of these were prescribed LABAs as separate inhalers.[6] Among those patients prescribed LABAs as separate inhalers, 6% of patients were not prescribed any ICS throughout the year (described as sustained LABA monotherapy) while an additional 12% of patients had significant gaps in ICS prescribing (described as episodic monotherapy). These findings mean that approximately one in five patients who were prescribed LABAs as separate inhalers in primary care were exposed to the serious risks associated with LABA monotherapy. Much of this occurred despite regular medical review because although primary care asthma reviews were associated with a 66% reduction in sustained LABA monotherapy, they did not appear to influence the occurrence of episodic monotherapy which is primarily caused by non-adherence to ICS therapy.

"... approximately one in five patients who were prescribed LABAs as separate inhalers in primary care were exposed to the serious risks associated with LABA monotherapy."

WHY DOES LABA MONOTHERAPY OCCUR?

When LABAs and ICS are prescribed in separate inhalers, LABA monotherapy will occur if symptom control is achieved and patients subsequently fail to adhere to ICS. Non-adherence to ICS therapy in asthma is common, can affect up to 60% of patients and is associated with a higher morbidity from asthma.[7,8] The reasons for non-adherence to ICS therapy in asthma are complex and may range from concerns over steroid side effects, complex treatment regimens, or difficulties in recognising asthma symptoms, all of which may prompt discontinuation of ICS therapy once symptom control is thought to be achieved. Although there is clearly a need for better interventions aimed at improving adherence to ICS it seems unlikely that patient education targeted at reinforcing the risks associated with LABA monotherapy will completely prevent non-adherence to ICS and the subsequent risk of LABA monotherapy.

This recent study also looked at other factors associated with LABA monotherapy and found that gaps in ICS prescribing occurred less often among patients registered with dispensing practices. Differential rates of ordering among patients may be more visible to dispensing practices, prompting feedback or a review of their medication. If this is indeed the case, a community pharmacy-based intervention may be an effective strategy for reinforcing adherence to ICS therapy among patients with asthma providing that continuity of care is maintained and shared. Furthermore, practice-based strategies could focus on improved methods of electronic detection, monitoring, and feedback of high risk reliever and preventer medication use among people with asthma in order to improve adherence to ICS and subsequent clinical outcomes.

A SOLUTION TO THE PROBLEM

However, in practice the only sure way to avoid the excess risk associated with LABA monotherapy in people with asthma is to prescribe a combination inhaler containing both LABA and ICS. This has the additional advantage of not only improving adherence to ICS but also of reducing treatment burden in asthma.[9] A perceived disadvantage of prescribing LABAs/ICS combination inhalers is the lack of flexibility in ICS dose-titration. However, a pragmatic approach of simpler treatment regimens with improved ICS adherence (and associated clinical outcomes) is likely to outweigh any potential benefits of fine-tuning ICS therapy with separate inhalers when problems of non-adherence are widespread. A further perceived disadvantage is the increased cost of combination inhalers. Despite the higher individual drug costs associated with combination inhalers evidence suggests that in patients with asthma uncontrolled on ICS, the combination of LABA and ICS in a single inhaler is a cost-effective

"... the only sure way to avoid the excess risk associated with LABA monotherapy in people with asthma is to prescribe a combination inhaler containing both LABA and ICS."

strategy based on improvements in patient outcomes.[10] Moreover, the recent UK-based study of LABA prescribing in asthma clearly shows that the vast majority (approximately three-quarters) of patients with asthma who used LABAs already received combination inhalers.[6]

FUTURE PERSPECTIVES

Although LABAs are only recommended for use with ICS, it is still uncertain whether some patients may be at increased risk of adverse events even with ICS therapy, because deaths from asthma in clinical trials are rare. In response to this uncertainty, the US Food and Drug Administration (FDA) have mandated that manufacturers of LABAs conduct large safety trials of LABA/ICS combination therapy which are due for completion in 2017.[11] In the meantime, there is a clear argument for preventing LABA monotherapy in asthma and this recent study on LABA prescribing in primary care supports the current BTS/SIGN recommendation that LABA/ICS therapy should only be prescribed in combination inhalers. It is now important to ensure that changes in guidelines translate into clinical practice by stopping the prescribing of LABAs in separate inhalers for asthma.

Daniel R Morales,
Clinical Academic Fellow, Division of Population Health Sciences, Medical Research Institute, University of Dundee, Dundee.

Provenance
Commissioned; externally peer reviewed.

Funding
The Scottish Government Chief Scientist Office Clinical Academic Fellowship scheme provided support for Daniel Morales and had no influence on the publication of the work.

Competing Interests
The author has declared no competing interests.

DOI: 10.3399/bjgp13X675250

ADDRESS FOR CORRESPONDENCE

Daniel R Morales
Division of Population Health Sciences, Medical Research Institute, University of Dundee, Mackenzie Building, Dundee, DD2 4BF.

E-mail: d.r.z.morales@dundee.ac.uk

REFERENCES

1. British Thoracic Society, Scottish Intercollegiate Guidelines Network (SIGN). *British Guideline on the Management of Asthma. SIGN Guideline No 101.* Edinburgh: SIGN, 2012.
2. Lipworth BJ. Antagonism of long-acting beta2-adrenoceptor agonism. *Br J Clin Pharmacol* 2002; **54(3):** 231–245.
3. Nelson HS, Weiss ST, Bleecker ER, *et al.* The Salmeterol Multicentre Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. *Chest* 2006; **129:** 15–26.
4. MHRA drug safety update. Long-acting β2-agonists: reminder for use in children and adults. 2010. http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON093845 (accessed 15 Nov 2013).
5. British Thoracic Society, Scottish Intercollegiate Guidelines Network (SIGN). British guideline on the management of asthma. *Thorax* 2008; **63(Suppl 4):** iv1–21.
6. Morales D, Jackson C, Fielding S, Guthrie B. Long-acting β-agonist prescribing in people with asthma in primary care. *Thorax* 2013; **68(2):** 192–194.
7. van Staa TP, Cooper C, Leufkens HG, *et al.* The use of inhaled corticosteroids in the United Kingdom and the Netherlands. *Respir Med* 2003; **97(5):** 578–585.
8. Williams LK, Pladevall M, Xi H, *et al.* Relationship between adherence to inhaled corticosteroids and poor outcomes among adults with asthma. *J Allergy Clin Immunol* 2004; **114:** 1288–1293.
9. Stempel DA, Stoloff SW, Carranza Rosenzweig JR, *et al.* Adherence to asthma controller medication regimens. *Respir Med* 2005; **99(10):** 1263–1267.
10. Bahadori K, Quon BS, Doyle-Waters MM, *et al.* A systematic review of economic evaluations of therapy in asthma. *J Asthma Allergy* 2010; **3:** 33–42.
11. FDA drug safety communication. FDA requires post-market safety trials for Long-Acting Beta-Agonists (LABAs). April 2011. http://www.fda.gov/Drugs/DrugSafety/ucm251512.htm (accessed 15 Nov 2013).