

# Increasing compliance with inhaled corticosteroids through the use of combination therapy

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Long-term treatment of chronic conditions invariably leads to poor compliance. By whatever definition used, levels of compliance with the use of inhaled medications in the treatment of asthma are poor, being in the range of 40% to 50%,<sup>1,2</sup> with values as low as 15% having been reported.<sup>3</sup> Studies of cases of fatal and life-threatening asthma consistently identify poor compliance with treatment as a strong risk factor.<sup>4</sup> It has been shown that better compliance with inhaled corticosteroid (ICS) therapy improves clinical outcomes and reduces the risk of asthma death.<sup>5,6</sup> Improving compliance involves many approaches, including patient education, patient participation in their medical care, frequent medical review, and simplification of treatment regimes as much as possible. One way to achieve the latter would be to reduce the number of different inhalers that need to be taken.

The use of both ICS and long-acting  $\beta$ -agonist (LABA) therapy is accepted as the most effective treatment regime to control moderate and severe asthma.<sup>7</sup> Recently, combination inhalers that contain both of these medications in a single device have become available. There are three main advantages of having both medications in one inhaler. First, there is an improved safety profile, as patients are not able to take their LABA therapy without concomitant ICS therapy. There have been safety concerns regarding the use of LABA as sole therapy, and guidelines have cautioned strongly against such a regime.<sup>8</sup>

Second, there are reports of synergy when both drugs are delivered from one inhaler device, at least with Seretide/Advair combination therapy containing salmeterol and fluticasone. The additional benefits have been attributed to particle agglomeration of salmeterol and fluticasone, resulting in codeposition in the airways,<sup>9,10</sup> thereby enhancing the synergistic interaction between the  $\beta$ -agonist and corticosteroid at the receptor level.<sup>11,12</sup> A recent meta-analysis reported in the *Journal* has suggested that the synergy may be of clinical significance with the odds of achieving a 30 L/min improvement in morning peak flow with combination therapy increased by approximately 40% compared with a regime based on separate inhalers.<sup>9</sup>

Third, it would be expected that the use of combination therapy should improve compliance with ICS therapy as its use is linked with LABA therapy, which patients are more likely to take because of the greater symptomatic benefit. In asthma, compliance is primarily a problem with ICS therapy partly because of the perception that it does not provide immediate benefit, unlike inhaled bronchodilator therapy. It is also widely recognized that adherence to treatment in asthma declines as the regime becomes more complicated, either by increasing the number of medications and/or the number of daily doses.<sup>13,14</sup> As a result, improved compliance would be expected to occur through the use of a single combination inhaler simply because of the reduction in the number of medications and actuations required with such a regime. Although this advantage has consistently been proposed for combination therapy, an increase in compliance has not until now been convincingly demonstrated.

Methods for assessing asthma inhaler compliance include patient self-reporting in diaries and weighing of used canisters, but both of these methods may be grossly inaccurate. Covert electronic monitoring of inhalers is the gold standard, but these studies require specialized electronic devices and so only a few small such studies have been undertaken.<sup>15,16</sup> Another approach that is more applicable to the "real world" situation is the assessment of patient medication refill persistence over prolonged periods as a measure of compliance and/or adherence.

This method has been used in the study by Stoloff et al that appears in this issue of the *Journal*, using a medical and pharmacy claims database from a large managed-care organization.<sup>17</sup> They observed that patients who took the fluticasone/salmeterol combination inhaler had significantly higher prescription refill rates than patients taking fluticasone alone or fluticasone and salmeterol from separate inhalers. The magnitude of the differences in drug utilization was considerable, as shown by the 72% to 79% greater use of fluticasone from the combination inhaler compared with the fluticasone single-inhaler regimes. There was also indirect evidence that this greater compliance resulted in improved asthma control, with patients using the combination inhaler having the lowest use of short-acting  $\beta$ -agonists. This would be consistent with studies that have shown that improved compliance with ICS therapy, as measured by refill persistence, is associated with decreased risk of morbidity and mortality from asthma.<sup>5,6</sup>

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While recognizing the limitations of the Stoloff et al study, it does provide the first substantive evidence that the use of ICS/LABA therapy from a combination inhaler improves compliance and that this may contribute to the improved asthma control obtained with combination therapy in general practice. A large, well-designed study with covert electronic monitoring could put this issue beyond doubt if it accurately quantified both the magnitude of increase in compliance and the associated improvement in asthma outcomes.

## REFERENCES

1. Chmelik F, Doughty A. Objective measurements of compliance in asthma treatment. *Ann Allergy* 1994;73:527-32.
2. Yeung M, O'Connor SA, Parry DT, Cochrane GM. Compliance with prescribed drug therapy in asthma *Respir Med* 1994;88:31-5.
3. Rand CS, Wise RA, Nides M, Simmons MS, Bleecker ER, Kusek JW, et al. Metered-dose inhaler adherence in a clinical trial. *Am Rev Respir Dis* 1992;146:1559-64.
4. Rea HH, Scragg R, Jackson R, Beaglehold R, Fenwick J, Sutherland DC. A case-control study of deaths from asthma. *Thorax* 1986;41:833-9.
5. Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B. Low-dose inhaled corticosteroids and the prevention of death from asthma. *N Engl J Med* 2000;343:332-6.
6. Suissa S, Ernst P, Kezouh A. Regular use of inhaled corticosteroids and the long-term prevention of hospitalization for asthma. *Thorax* 2002;57:880-4.
7. Barnes PJ. Scientific rationale for inhaled combination therapy with long-acting  $\beta_2$ -agonists and corticosteroids. *Eur Respir J* 2002;19:182-91.
8. Global Initiative for Asthma. Global strategy for asthma management and prevention. Bethesda, Md: National Institutes of Health, National Heart Lung and Blood Institute, 2002. NIH Publication No. 02-3659.
9. Nelson HS, Chapman KR, Pyke SD, Johnson M, Pritchard JN. Enhanced synergy between fluticasone propionate and salmeterol inhaled from a single inhaler versus separate inhalers. *J Allergy Clin Immunol* 2003;112:29-36.
10. Michael Y, Snowden MJ, Chowdrey BZ, Ashurst IC, Davies-Cutting C, Riley T. Characterisation of the aggregation behaviour in a salmeterol and fluticasone propionate inhalation aerosol system. *Int J Pharm* 2001;221:165-74.
11. Mak JC, Nishikawa M, Barnes PJ. Glucocorticoids increase  $\beta_2$ -adrenergic receptor transcription in human lung. *Am J Physiol* 1995;268:L41-6.
12. Baranuik JN, Ali M, Brody D, Maniscalco J, Gaumond E, Fitzgerald T, et al. Glucocorticoids induce  $\beta_2$ -adrenergic receptor function in human nasal mucosa. *Am J Respir Crit Care Med* 1997;155:704-10.
13. Coutts JAP, Gibson NA, Paton JY. Measuring compliance with inhaled medication in asthma. *Arch Dis Child* 1992;67:332-3.
14. Chapman KR, Walker L, Cluley S, Fabbri L. Improving patient compliance with asthma therapy. *Respir Med* 2000;94:2-9.
15. Bosley CM, Parry DT, Cochrane GM. Patient compliance with inhaled medication: does combining beta-agonists with corticosteroids improve compliance? *Eur Respir J* 1994;7:504-9.
16. Simmons MS, Nides MA, Kleerup EC, Chapman KR, Milgrom H, Rand CS, et al. Validation of the Doser, a new device for monitoring metered-dose inhaler use. *J Allergy Clin Immunol* 1998;102:409-13.
17. Stoloff SW, Stempel DA, Meyer J, Stanford RH, Carranza Rosenzweig JR. Improved refill persistence with fluticasone propionate and salmeterol in a single inhaler compared with other controller therapies. *J Allergy Clin Immunol* 2004;113:245-51.