



# Critical Appraisal

## Flexible asthma therapy

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Aalbers R, Backer V, Kava TT, Omenaas ER, Sandstrom T, Jorup C, et al. Adjustable maintenance dosing with budesonide/formoterol compared with fixed-dose salmeterol/fluticasone in moderate to severe asthma. *Curr Med Res Opin* 2004;20(2):225-40.

### Research question

Is adjustable maintenance dosing with budesonide/formoterol (B/F) more effective in gaining and maintaining asthma control than fixed dosing with salmeterol/fluticasone (S/F)?

### Type of article and design

Prospective, randomized, double-dummy, double-blind with open extension, parallel-group study conducted at 93 outpatient clinics in Europe.

### Relevance to family physicians

Asthma is one of the most common chronic conditions encountered by family physicians. In the 1990s, it was discovered that adding a long-acting beta-2-agonist to inhaled corticosteroids (ICS) provided more effective asthma control than higher doses of ICS in patients with mild-to-severe disease.<sup>1-4</sup> Two studies<sup>3,4</sup> involving B/F at fixed doses were the first to demonstrate in a prospective fashion that severe exacerbation rates decreased significantly.

Current asthma guidelines support use of action plans that guide patients to adjust their medications based on level of asthma control,<sup>5</sup> such that asthma control is maintained using the lowest effective

dose. Asthma's variability<sup>5</sup> means asthma control can fluctuate over time, necessitating flexible therapy. Studies<sup>6,7</sup> suggest that physician-guided self-management plans involving partnerships between patients and doctors can improve asthma control and reduce the need for oral steroids.

Currently in Canada, two dry-powder combination products are available in a single inhaler: B/F (Symbicort Turbuhaler) and S/F (Advair Diskus). Given that the dose-response curve of salmeterol is relatively flat above 50 µg,<sup>8</sup> patients need a separate inhaler to increase the dose of ICS with use of the Advair Diskus. Dose of B/F can be varied using the same inhaler for from one to four inhalations twice daily, making it suitable for adjustable maintenance dosing and part of a flexible action plan.

### Overview of study and outcomes

This study involved symptomatic patients with asthma (n = 658) taking a mean of 735 µg of ICS each day and having a forced expiratory volume in 1 second (FEV<sub>1</sub>) of 84% of predicted. After a 2-week run-in period, patients were randomized to B/F using adjustable maintenance dosing, B/F at fixed doses, or S/F at fixed doses for 4 weeks at doses of 320/9.0, 320/9.0, and 50/250 µg twice daily, respectively. This was followed by a 6-month open-label extension. Patients in the B/F adjustable maintenance dosing group with well controlled asthma were allowed to lower their doses to 160/4.5 µg twice daily. All patients in the adjustable maintenance dosing group were allowed to

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increase their doses to 720/18 µg twice daily for 7 to 14 days if symptoms worsened.

Patients were allowed to use turbutaline or salbutamol for symptom relief. The primary outcome variable was the odds of achieving a well controlled asthma week: a week with no nighttime awakening due to asthma, no exacerbations, and no change in asthma treatment due to adverse events, plus at least two of an asthma symptom score of  $>1$  on  $\leq 2$  days;  $\leq 2$  days of relief medication use; and a morning peak expiratory flow rate  $\geq 80\%$  of predicted normal every day. Exacerbations were defined as the need for oral steroid therapy for  $\geq 3$  days, emergency room visits, or hospitalization due to asthma.

Using normal approximation methods, the study was powered to 80% to detect an odds ratio of 1.41. The total number of asthma exacerbations was compared between groups using a Poisson regression method.

### Results

The odds of achieving a well controlled asthma week over the whole treatment period were similar for B/F and S/F at fixed doses. Patients taking B/F using adjustable maintenance dosing, however, had a lower exacerbation rate over the study, 40% lower than patients taking S/F at fixed doses ( $P = .018$ ). Patients taking B/F using adjustable maintenance dosing used less relief medication in the open extension (0.58 occasions daily) than patients taking B/F at fixed doses (0.92 occasions daily,  $P = .001$ ) and than patients taking S/F at fixed doses (0.80 occasions daily,  $P = .011$ ).

### Analysis of methodology

This study compared treatment strategies and thus lacked a control group. Having a placebo-control group would pose ethical issues given the benefits

reported for the treatment regimens studied. A limitation of the study is the lack of blinding in the 6-month open-label extension. A double-blind, double-dummy design for the adjustable maintenance dosing arm would have required a very complex design with at least four inhalers per treatment arm, a design that would be less applicable to real-life clinical situations.

The patients studied qualified for combination therapy based on the severity of their symptoms and their lung function, and they were recruited from outpatient clinics. Results of this trial should be applicable to the types of patients encountered in primary care. The written action plan and instruction on its use in the adjustable maintenance dosing arm is recommended by current guidelines and encourages interaction between patients and physicians, a strategy that has been shown to improve asthma control.<sup>6,7</sup>

### Application to clinical practice

This study underscores the benefits of adjusting combination therapy (B/F) when asthma symptoms worsen using a self-management strategy in the form of a written action plan. For this approach, the Turbuhaler is more convenient than the Advair Diskus. The well controlled asthma week might not be the most relevant composite treatment outcome since many patients did not achieve this target. Longer-term studies are required to determine whether treatment benefits are maintained over time.

### Bottom line

- Adjustable maintenance dosing with budesonide/formoterol reduces asthma exacerbations more effectively than fixed dosing with salmeterol/fluticasone.
- The adjustable maintenance dosing strategy encourages patients to have a proactive role in self-management.
- The adjustable maintenance dosing strategy using a Turbuhaler is simple and does not require additional inhalers to adjust the dose of ICS in response to changes in asthma control.

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- Head-to-head studies comparing adjustable maintenance dosing using the Advair Diskus and the Symbicort Turbuhaler are needed. ❁

### Points saillants

- Le dosage ajustable d'entretien à base de budesonide /formotérol réduit plus efficacement l'exacerbation de l'asthme que le dosage fixe de salmétérol/fluticasone.
- La stratégie thérapeutique de dosage ajustable d'entretien encourage le patient à exercer un rôle proactif dans sa propre prise en charge.
- La stratégie thérapeutique de dosage ajustable d'entretien à l'aide d'un Turbuhaler est simple et n'exige pas d'autre inhalateur pour ajuster la dose de corticostéroïdes inhalés en réponse à des changements dans le contrôle de l'asthme.
- Il faut procéder à des études comparant directement le dosage ajustable d'entretien à l'aide du Advair Diskus et du Symbicort Turbuhaler.

### Acknowledgment

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