

Is the maintenance and reliever approach the answer?

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Objective: To examine the efficacy of the maintenance and reliever (M+R) approach in the treatment of asthma exacerbations.

Data Sources: PubMed, MEDLINE, and Cochrane database searches using the key words *formoterol* and *budesonide*, *dynamic dosing*, *adjustable dosing*, and *M+R therapy*.

Study Selection: Articles were selected based on their relevance to the topic of this review.

Results: Several studies have examined dynamic dosing of the long-acting β -agonist formoterol combined with budesonide in the treatment of asthma. Most of these studies have shown reductions in asthma exacerbations. Although obvious concern arises regarding increase in dose of the long-acting β -agonist component, no significant signal of morbidity or mortality has been seen. Potential concerns regarding the studies performed thus far include the fact that all have been sponsored by the pharmaceutical industry and have required β -agonist response as an inclusion criterion.

Conclusions: Although many of the data regarding this approach are positive, not all the studies have demonstrated efficacy. It is hoped that future non-pharmaceutical company-sponsored research will clarify this issue and, should efficacy be confirmed, shed light on the mechanism of action.

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INTRODUCTION

According to the 2007 National Asthma Education and Prevention Program Expert Panel Report 3,¹ asthma is a common yet complex chronic disorder of the airways characterized by variable and recurring symptoms, airflow obstruction, bronchial hyperresponsiveness, and underlying inflammation. Characteristic symptoms of asthma include dyspnea, chest tightness, wheeze, and often cough. Despite national and

international efforts to improve the accuracy of the diagnosis of asthma, its evaluation, and patient education with appropriate approaches to therapy, asthma control remains suboptimal.

This study was performed to examine the efficacy of the maintenance and reliever (M + R) approach in the treatment of asthma exacerbations. We searched the PubMed, MEDLINE, and Cochrane databases using the key words *formoterol* and *budesonide*, *dynamic dosing*, *adjustable dosing*, and *M + R therapy*. Articles were selected based on their relevance to the topic of this review. One reason for suboptimal asthma control is the intrinsic variability inherent in asthma. For example, Calhoun and colleagues² highlighted the intrinsic variability in asthma by studying a group of patients with moderate to severe persistent asthma who had been randomized to the placebo arm of a double-blind, placebo-controlled trial. Through 12 weeks, more than 50% of the patients changed their severity classification. This lability is characteristic of mild and severe asthma and may portend disastrous outcomes. Robertson et al³ reported that approximately one-third of pediatric patients who died of asthma had previously been categorized as having mild disease.

Nonadherence with the use of asthma controller medications is another important component associated with increased asthma morbidity and mortality. Retrospective analyses of controller medication use suggest that many asthmatic individuals use only approximately 3 of an expected 12 canisters of inhaled corticosteroid (ICS) per year and slightly more than 4 of an expected 12 canisters of combined long-acting β -agonist (LABA)–ICS per year.⁴ These data are of

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concern because reduced adherence to ICS treatment has been reported to be associated with increased asthma mortality.⁵ Even after discharge from the hospital after an exacerbation, adherence is poor; a 50% reduction in adherence to ICSs and oral corticosteroids (OCSs) has been observed in the week after discharge.⁶ Compounding issues in patient adherence is the fact that patients adjust their dose or asthma medicines when faced with increased symptoms and that they do so in an ineffective manner.⁷

APPROACHES TO DYNAMIC MEDICATION ADJUSTMENT IN ASTHMA

In light of the dynamic nature of asthma symptoms and control, dynamic medication adjustment seems to be a reasonable approach to disease management. Several alternative strategies have been tried to manage deteriorating asthma control. Because asthma exacerbations have been associated with an increase in inflammation, it is reasonable to suggest that an increase in ICS dose would be an effective treatment strategy. However, doubling the ICS dose during an asthma exacerbation has been proved to be ineffective.⁸ Conversely, increasing to 5-fold dose escalation of ICS proved to be effective, although the data supporting this strategy are limited.⁹

One possible reason for the lack of efficacy (or the limited efficacy) of these treatment strategies could be the kinetics of the increase in symptoms in relation to the exacerbation per se. As per data from the FACET (Formoterol and Corticosteroids Establishing Therapy), Tattersfield and colleagues¹⁰ reported that there is a delay in the peak of asthma symptoms from their onset of approximately 5 days. This observation was replicated by the International Asthma Patient Insight Research INSPIRE (Investigating New Standards for Prophylaxis in Reduction of Exacerbations) study. In this study, the authors relied on structured interviews of 3,415 adult patients with physician-diagnosed asthma requiring long-term maintenance therapy with ICSs or ICSs and LABAs. Beyond noting a multiday delay in the peak of asthma symptoms from their onset, they also found that patients most commonly responded by increasing their short-acting β -agonist dose immediately and delaying increasing their ICS dose.⁷ Strategies to increase the dose of an effective controller therapy early in the deterioration of asthma control might prove to be a more effective approach to this dilemma.

In response to this need, investigators have examined the potential role of different technologies to help guide asthma management. The most studied of these include home peak flow meters and in-office measurement of exhaled nitric oxide. Although the use of home peak flow monitoring has been standard in asthma care recommendations, a recent large prospective study by Buist et al¹¹ demonstrated that the addition of peak flow measurements provided no added benefit to standard symptom-based care. Several studies have demonstrated adjustment of therapy based on sputum eosinophil counts is a useful noninvasive inflamometer; however, this procedure is not feasible for most physicians.¹² Thus, after an

initial positive study and the introduction of several Food and Drug Administration–approved devices that are not cost prohibitive, many specialists expressed great enthusiasm regarding the addition of exhaled nitric oxide measurement in the office.¹³ However, a large-scale prospective study¹⁴ failed to demonstrate any added benefit with the use of exhaled nitric oxide–guided care compared with standard National Heart, Lung, and Blood Institute guideline–directed care. Such tools are likely to be useful, however, in the subgroup of asthmatic individuals who are poor perceivers of dyspnea, although this group is a minority.¹⁵

COMBINATION OF ICSs AND RAPID-ONSET LABAs FOR MAINTENANCE AND RELIEVER THERAPY FOR ASTHMA

Several studies have examined dynamic dosing of the LABA formoterol combined with budesonide in the treatment of asthma, that is, for maintenance and rescue treatment (M+R approach). These studies have shown reductions in asthma exacerbations and have resulted in the European Union Authority's approval of this modality of therapy. We explore this research in more detail herein.

Controlled Trials

The effectiveness of the M+R approach is well illustrated by O'Byrne and colleagues,¹⁶ who performed a yearlong, double-blind, randomized, parallel-group study involving 2,760 patients with asthma aged 4 to 80 years (forced expiratory volume in 1 second [FEV₁], 60%-100% of predicted) who were randomized to receive budesonide-formoterol, 80/4.5 μ g twice a day, with terbutaline, 0.4 mg, as rescue therapy; budesonide, 320 μ g twice a day, with terbutaline, 0.4 mg, as rescue therapy; or budesonide-formoterol, 80/4.5 μ g twice a day, with 80/4.5 μ g as needed for rescue (children used a once-nocturnal maintenance dose). The M+R approach resulted in a prolonged time to first severe exacerbation (defined as deterioration in asthma resulting in a morning peak expiratory flow rate of 70% or less of baseline on 2 consecutive days, hospitalization or an emergency department [ED] visit, or an increase in the ICS dose or a need for OCSs [$P < .001$]); prolonged the time to the first, second, and third exacerbations requiring medical intervention ($P < .001$); and improved symptoms, nocturnal awakenings, and lung function.¹⁶

Rabe and colleagues¹⁷ similarly examined the efficacy of the M+R approach in a 12-month, double-blind, parallel-group study of 3,394 patients (aged ≥ 12 years) who were symptomatic while taking budesonide-formoterol (160/4.5 μ g), 1 inhalation twice daily, during a 2-week run-in by randomly assigning patients to budesonide-formoterol maintenance therapy and comparing the efficacy and safety of 3 reliever strategies: (1) a traditional short-acting β_2 -agonist, (2) the rapid-onset LABA formoterol, and (3) a combination of a LABA and an ICS (budesonide-formoterol). Time to the first severe exacerbation (defined previously herein) was delayed with as-needed M+R budesonide-formoterol vs for-

moterol ($P = .005$; log-rank test) and with as-needed formoterol vs terbutaline ($P = .005$).¹⁷ The rate of severe exacerbations was 37, 29, and 19 per 100 patients per year with as-needed terbutaline, formoterol, and budesonide-formoterol, respectively (rate ratios: budesonide-formoterol vs formoterol, 0.67 [95% confidence interval (CI), 0.56-0.80; $P < .001$]; budesonide-formoterol vs terbutaline, 0.52 [95% CI, 0.44-0.62; $P < .001$]; and formoterol vs terbutaline, 0.78 [95% CI, 0.67-0.91; $P = .001$]). Asthma control days were similar among all groups.

Unblinded Observations

In an unblinded study attempting to more closely mimic a real-world scenario, Vogelmeier and colleagues¹⁸ performed a 12-month dose-titration study in 2,143 adolescents and adults comparing the effectiveness of budesonide-formoterol (160/4.5 μg) for M+R with a control group using fluticasone-salmeterol (250/50 μg) for maintenance plus salbutamol for relief. The M+R prolonged the time to first severe exacerbation (defined as deterioration in asthma resulting in hospitalization or an ED visit, OCS use for 3 or more days, or an unscheduled office visit leading to treatment change) vs salmeterol-fluticasone (25% risk reduction), with the total number of severe exacerbations significantly reduced in the budesonide-formoterol group (255 vs 329).¹⁸ Both regimens provided sustained improvements in symptoms, as-needed use of rescue therapy, quality of life, and FEV₁, with differences in favor of the M+R for as-needed use (0.58 vs 0.93 inhalations daily) and FEV₁ (post- β_2 -agonist values). The mean ICS dose during treatment was similar in both groups (653 mg of budesonide per day [M+R] vs 583 mg of fluticasone per day).

Observations in Children

Finally, in a 12-month, double-blind, randomized pediatric study of 341 children (aged 4-11 years) with asthma uncontrolled with ICSs alone, Bisgaard et al¹⁹ examined whether budesonide-formoterol as M+R therapy could reduce exacerbations by comparing budesonide-formoterol, 80/4.5 μg once daily, maintenance plus additional inhalations for symptom relief with fixed combination budesonide-formoterol, 80/4.5 μg once daily, for maintenance with terbutaline rescue vs higher-dose budesonide, 320 μg once daily, with terbutaline rescue. The M+R approach resulted in a prolonged time to first exacerbation (defined as a deterioration in asthma resulting in hospitalization or ED treatment, treatment with OCSs, an increase in ICSs [via a separate inhaler, ie, not study medication], any other additional treatment, or a morning peak expiratory flow rate of 70% or less of the baseline mean on 2 consecutive days) compared with fixed-dose budesonide ($P = .02$) and fixed-dose combination ($P < .001$). The rates of exacerbation requiring medical intervention were reduced by 70% to 79% with M+R vs fixed-dose budesonide and fixed-dose combination (0.08 per patient vs 0.28 and 0.40 per patient, respectively; $P < .001$ for both). Mild exacerbation days and nocturnal awakenings were sig-

nificantly lower with M+R, and yearly growth improved by 1.0 cm vs fixed-dose budesonide ($P < .01$).

Negative Studies

Tempering enthusiasm seen from the previous studies are some data that failed to demonstrate benefit from the M+R approach. In a study by Bousquet et al,²⁰ 2,309 symptomatic asthmatic patients who experienced an asthma exacerbation in the previous year were randomized to receive budesonide-formoterol (160/4.5 μg), 2 inhalations twice daily and as needed, or 1 inhalation of fluticasone-salmeterol (500/50 μg) twice daily with terbutaline as needed for 6 months. The primary outcome of this study, time to first severe exacerbation (defined as deterioration in asthma resulting in hospitalization or an ED visit or OCSs being required for ≥ 3 days), was not significantly prolonged in the M+R group (risk ratio: 0.82; 95% CI, 0.63-1.05); however, they did demonstrate that the M+R approach reduced total exacerbations from 31 to 25 per 100 patients per year ($P = .04$) and exacerbations requiring hospitalization or ED treatment from 13 to 9 per 100 patients per year ($P = .046$). Regarding measures of control, no differences in the number of asthma control days, Asthma Control Questionnaire scores (5-question version), or lung function were demonstrated between the groups.

In a study by FitzGerald and colleagues,²¹ 688 asthmatic patients underwent a randomized, double-blind, double-dummy, parallel-group study comparing similar doses of fluticasone-salmeterol twice daily (250/50 μg) with budesonide-formoterol via the M+R approach (400/12 μg) for 1 year. In this study, the M+R approach demonstrated inferiority to the stable-dose intervention in the primary end point of symptom-free days (defined as no symptoms during a 24-hour period) ($P = .034$) and in the annual exacerbation rate (defined as worsening asthma requiring hospital treatment or treatment with OCSs) ($P = .008$).

Finally, in a recent Cochrane meta-analysis, Cates and Lasserson²² examined not only the previously mentioned studies but also others in abstract form only or not yet published (such as the MONO [Symbicort single inhaler therapy and conventional best standard treatment for the treatment of persistent asthma in adolescents and adults] and SALTO [symbicort single inhaler therapy use in adolescent adults and adults with persistent asthma] trials) and found lack of added benefit comparing the M+R approach with standard therapy. When examining the end point of asthma exacerbations that require an OCS in adults, data from 4,470 patients were unable to demonstrate significant reduction when using the M+R approach (153 exacerbations in 2,244 patients in M+R therapy vs 181 exacerbations in 2,226 patients in standard care; odds ratio [OR], 0.83; 95% CI, 0.66-1.03). Likewise, when examining the outcome of severe exacerbations that require medical intervention, lack of benefit was seen (hazard ratio, 0.96; 95% CI, 0.85-1.07). Regarding adverse events, this meta-analysis demonstrated no significant differences in fatal and serious nonfatal outcomes (fatal events: OR, 1.95; 95% CI, 0.39-9.67; and nonfatal

events: OR, 1.02; 95% CI, 0.68-1.52). The authors, however, highlight that the overall number of events was too small to rule out the possibility of a clinically significant impact.

LABA USE AND ADVERSE ASTHMA OUTCOMES

Concerns have been voiced about the use and potential overuse of LABAs, particularly as monotherapy, since their early approval. Many of these concerns involve the use of LABAs for maintenance therapy and in doses approved for use in the United States. In a Letter to the Editor of the *New England Journal of Medicine*, Finkelstein²³ described 2 elderly asthmatic patients who died while “clutching their (LABA) inhalers.” These fears have been reinforced after publication of the recent SMART (Salmeterol Multicenter Asthma Research Trial) study,²⁴ the meta-analysis by Salpeter and colleagues,²⁵ and the *New England Journal of Medicine* opinion piece by Martinez.²⁶

As for a potential mechanism for any deleterious effect, some researchers have suggested that this is a result of the LABA masking underlying inflammation. In a crossover study, McIvor et al²⁷ studied 13 patients who required a median dose of 2,700 μg of ICS who underwent an ICS taper while being treated with concomitant salmeterol or placebo until exacerbation of asthma occurred. Peak expiratory flow rate and symptoms were measured daily, and sputum eosinophils, methacholine reactivity, eosinophil cationic protein, and spirometry were assessed weekly. At the time of exacerbation, the LABA arm was using a median dose of ICS of 277 μg compared with 612 μg of ICS in the placebo group. This reduction in ICS came at the cost of an increase in sputum eosinophil counts (19.3%) in the LABA group compared with the placebo group (9.3%) at the time of exacerbation ($P = .006$). Note, however, that at the time of exacerbation in the group receiving the LABA, almost half (6 of 13) of the patients were not taking an ICS at all. Concern may arise that this increase in LABA dose may result in an increase in morbidity or mortality.

Regarding evaluation of higher-than-usual doses of LABA, Mann and colleagues²⁸ reported in a meta-analysis of 3 studies submitted to the Food and Drug Administration that more patients treated regularly with formoterol, 24 μg twice daily, had a serious asthma exacerbation than did those treated with placebo. When considering this study, note that patients were not receiving concomitant ICSs. Thus, as demonstrated in the study by McIvor et al,²⁷ it is possible that using the LABA as high-dose monotherapy may have resulted in masking of inflammation and, therefore, allowed a greater level of exacerbation, resulting in the seriousness of the event.²⁵ A level of comfort can be gained by the fact that no signal has been seen in any of the M+R studies or in the Cochrane meta-analysis.²²

POSSIBLE MECHANISMS FOR THE SUCCESS OF M+R

Despite these potential concerns, many of the studies demonstrated that the M+R approach results in improved asthma

control. What are the reasons for this success? In truth, the mechanism is not known. Several studies²⁹⁻³¹ have demonstrated that LABAs do not provide demonstrable clinical anti-inflammatory effects. Thus, it is likely that the efficacy of this approach is the result of the increase in ICS dose. This may seem to be inconsistent with some observations because, as noted earlier, a double dose of ICS did not result in reduction of the exacerbation rate.⁸ Note, however, that in the double-dose study by FitzGerald et al⁸ there was a 48-hour delay in increasing the dose of ICS, and, because no immediate response to therapy was likely perceived by the patient, concern regarding adherence to increased dosing of ICS must be considered. Likewise, ICS dose frequency may have an impact. Toogood et al³² reported that more frequent dosing was associated with greater effect than was using the same quantity of ICS with less frequent dosing.

What mechanism(s) can one postulate regarding the quick response to ICS? The efficacy of corticosteroids can be stratified into 2 general categories: genomic and nongenomic. Genomic effects are delayed because they require the corticosteroid to enter the cell cytoplasm and to bind to the glucocorticosteroid receptor, followed by complex diffusing in the cell nucleus, binding to specific DNA sequences with resultant synthesis of messenger RNA and new protein molecules, with upregulation of anti-inflammatory effects and downregulation of proinflammatory effects.

Proposed nongenomic mechanisms that could be of importance in the prevention of exacerbations when ICSs are used as a reliever include a decrease in eosinophil infiltration, a decrease in vascular exudation, and a decrease in mucous production.³³ The rapidity of an ICS nongenomic effect was seen in a study by Gibson and colleagues³⁴ in which they demonstrated that after a single large dose of budesonide, a reduction in sputum eosinophils was observed. Because the driving force of M+R therapy from the patient perspective is the reliever component, they are more likely to begin additional ICS therapy when asthma control is just beginning to deteriorate, days before significant exacerbation were to begin. Thus, beyond nongenomic effects, genomic mechanisms might be operative to explain the effectiveness of M+R. Further research is needed to better delineate why the M+R approach works, such as whether there is some yet unknown effect from the LABA component or whether this simply is earlier and more frequent ICS dosing. With this knowledge, we may be able to better intervene during asthma exacerbations.

M+R AS AN AID IN ASTHMA SELF-MANAGEMENT

The M+R approach may have added utility because it has been shown that having a self-management plan can improve asthma-specific quality of life and may even enhance patient adherence.^{35,36} This concept is reinforced in the study by Partridge et al,⁷ in which most patients stated that they “disliked the uncertainty associated with asthma exacerbations, but felt confident about self-managing their asthma and intervening early by increasing their therapy.” As noted previ-

ously, they chose the wrong medicine to adjust immediately. When examining what components of the written action plan resulted in improvement in exacerbation outcomes, Gibson and Powell³⁷ found that the beneficial effects of an effective written action plan included the use of ICSs and OCSs. These studies reinforce the efficacy of the M+R approach in patients with moderate to severe asthma. It seems that it is the ICS component that provides the effectiveness of the M+R approach; however, the quick β_2 response seen in the combination therapy likely provides the patient with a level of confidence in the rescue medicine's efficacy and reinforces further use when needed throughout the period of decreased asthma control.

CONCLUSIONS

The M+R approach seems to be a step forward in the care of asthmatic patients and an important tool for decreasing asthma exacerbations. As outlined in a recent commentary by Barnes,³⁸ the beauty of a single combination maintenance and reliever inhaler (with a fast-acting β_2 -agonist and an ICS) is that it simplifies therapy and ensures use of the ICS, because patients will feel an immediate bronchodilating response. In a recent article in the *British Medical Journal*, Barnes³⁹ highlights the virtues of this method to primary care physicians. However, he suggests excluding patients who overuse their rescue inhalers or find it difficult to recognize asthma exacerbation. Two letters in response to Barnes' article deserve comment. Both letters reinforce concern regarding study design. In a letter by Hussain,⁴⁰ concern is voiced regarding the fact that all of the studies (positive and negative) are sponsored by pharmaceutical companies. He notes that patients who need more than 10 inhalations of rescue inhaler were excluded. Likewise, in a letter by Lipworth,⁴¹ it is pointed out that these studies selectively excluded patients who would not respond to a LABA as all of the subjects in these studies were required to demonstrate β_2 -agonist reversibility. Thus, in closing, we must acknowledge that we are losing the battle of adherence in the variable illness of asthma. Dynamic dosing of asthma therapy makes implicit sense, and the M+R approach seems appealing. Although many of the data regarding this method are positive, not all the studies have demonstrated efficacy. It is hoped that future non-pharmaceutical company-sponsored research will clarify this issue and, should efficacy be confirmed, shed light on the mechanism of action.

REFERENCES

1. National Heart, Lung, and Blood Institute, National Asthma Education and Prevention Program. Expert panel report 3: guidelines for the diagnosis and management of asthma: full report 2007. <http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf>. NIH publication 08-4051.
2. Calhoun W, Sutton L, Emmertt A, Dorinsky P. Asthma variability in patients previously treated with β_2 -agonists alone. *J Allergy Clin Immunol*. 2003;112:1088–1094.
3. Robertson CF, Rubinfeld AR, Bowes G. Pediatric asthma deaths in Victoria: the mild are at risk. *Pediatr Pulmonol*. 1992;13:95–100.
4. Stempel DA, Stoloff SW, Carranza Rosenzweig JR, et al. Adherence to asthma controller medication regimens. *Respir Med*. 2005;99:1263–1267.
5. Krishnan JA, Riekert KA, McCoy JV, et al. Corticosteroid use after hospital discharge among high-risk adults with asthma. *Am J Respir Crit Care Med*. 2004;170:1281–1285.
6. Suissa S, Ernst P, Benayoun S, et al. Low-dose inhaled corticosteroids and the prevention of death from asthma. *N Engl J Med*. 2000;343:332–336.
7. Partridge MR, van der Molen T, Myrseth S-E, Busse WW. Attributes and actions of asthma patients on regular maintenance therapy: the INSPIRE study. *BMC Pulm Med*. 2006;6(13):1–9.
8. FitzGerald JM, Becker A, Sears MR, et al. Doubling the dose of budesonide versus maintenance treatment in asthma exacerbations. *Thorax*. 2004;59:550–556.
9. Foresi A, Moreli MC, Catena E. Low dose budesonide with the addition of an increased dose during exacerbations is effective in long-term asthma control. *Chest*. 2000;117:440–446.
10. Tattersfield AE, Postma DS, Barnes PJ, et al. Exacerbations of asthma: a descriptive study of 425 severe exacerbations. *Am J Respir Crit Care Med*. 1999;160:594–599.
11. Buist AS, Vollmer WM, Wilson SR. A randomized clinical trial of peak flow versus symptom monitoring in older adults with asthma. *Am J Respir Crit Care Med*. 2006;174:1077–1087.
12. Green R, Brightling C, McKenna S, et al. Asthma exacerbations and sputum eosinophil counts: a randomized controlled trial. *Lancet*. 2002;360:1715–1721.
13. Smith AD, Cowan JO, Brassett KP, et al. Use of exhaled nitric oxide measurements to guide treatment in chronic asthma. *N Engl J Med*. 2005;352:2163–2173.
14. Szefer SJ, Mitchell Herman, Sorkness CA, et al. Management of asthma based on exhaled nitric oxide in addition to guideline-based treatment for inner city adolescents and young adults: a randomized controlled trial. *Lancet*. 2008;372:1065–1072.
15. Magadle R, Berar-Yanay N, Weiner P. The risk of hospitalization and near-fatal and fatal asthma in relation to the perception of dyspnea. *Chest*. 2002;121:329–333.
16. O'Byrne PM, Bisgaard H, Godard PP, et al. Budesonide-formoterol combination therapy as both maintenance and reliever medication in asthma. *Am J Respir Crit Care Med*. 2005;171:129–136.
17. Rabe KF, Atienza T, Magyar P, et al. Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomized controlled, double-blind study. *Lancet*. 2006;368:744–753.
18. Vogelmeier C, D'Urzo A, Pauwels R, et al. Budesonide-formoterol maintenance and reliever therapy: an effective asthma treatment option? *Eur Respir J*. 2005;26:819–828.
19. Bisgaard H, LeRoux P, Bijamer D, et al. Budesonide-formoterol maintenance plus reliever therapy: a new strategy in pediatric asthma. *Chest*. 2006;130:1733–1743.
20. Bousquet J, Boulet L, Peters MJ, et al. Budesonide/formoterol for maintenance and relief in uncontrolled asthma vs. high-dose salmeterol/fluticasone. *Respir Med*. 2007;101:2437–2446.
21. FitzGerald JM, Boulet L-P, Follows R. The CONCEPT trial: a 1-year, multicenter, randomized, double-blind, double-dummy comparison of a stable dosing regimen of salmeterol/fluticasone propionate with an adjustable maintenance dosing regimen of formoterol/budesonide in adults with persistent asthma. *Clin Ther*. 2005;27:393–406.
22. Cates CJ, Lasserson TJ. Combination formoterol and budesonide as maintenance and reliever therapy versus inhaled steroid maintenance for chronic asthma in adults and children. *Cochrane Database Syst Rev*. 2009;(2):CD007313.
23. Finkelstein FN. Risks of salmeterol? *N Engl J Med*. 1994;331:1314.
24. Nelson HS, Weiss ST, Bleecker ER, Yancey SW, Dorinsky PM. The Salmeterol Multicenter Asthma Research Trial (SMART): a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. *Chest*. 2006;129:15–26.

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25. Salpeter SR, Buckley NS, Ormiston TM, Salpeter EE. Meta-analysis: effect of long-acting β -agonists on severe asthma exacerbations and asthma-related deaths. *Ann Intern Med.* 2006;144:904–912.
 26. Martinez F. Safety of long-acting β -agonists: an urgent need to clear the air. *N Engl J Med.* 2005;353:2637–2639.
 27. McIvor RA, Pizzichini E, Turner MO, et al. Potential masking effects of salmeterol on airway inflammation in asthma. *Am J Respir Crit Care Med.* 1998;158:924–930.
 28. Mann M, Chowdhury B, Sullivan E, et al. Serious asthma exacerbations in asthmatics treated with high-dose formoterol. *Chest.* 2003;124:20–24.
 29. Roberts JA, Bradding P, Britten KM, et al. The long-acting β_2 -agonist salmeterol xinafoate: effects on airway inflammation in asthma. *Eur Respir J.* 1999;14:275–282.
 30. Lazarus SC, Boushey HA, Fahy JV, et al. Long-acting β_2 -agonist monotherapy vs continued therapy with inhaled corticosteroids in patients with persistent asthma: a randomized controlled trial. *JAMA.* 2001;285:2583–2593.
 31. Lemanske RF, Sorkness CA, Mauger EA, et al. Inhaled corticosteroid reduction and elimination in patients with persistent asthma receiving salmeterol: a randomized controlled trial. *JAMA.* 2001;285:2594–2603.
 32. Toogood J, Baskerville J, Jennings B, et al. Influence of dosing frequency and schedule on the response of chronic asthmatics to the aerosol steroid, budesonide. *J Allergy Clin Immunol.* 1982;70:288–298.
 33. Rodrigo GJ. Inhaled corticosteroids as rescue medication in acute severe asthma. *Expert Rev Clin Immunol.* 2008;4:723–729.
 34. Gibson PG, Salto N, Fakes K. Acute anti-inflammatory effects of inhaled budesonide in asthma: a randomized controlled trial. *Am J Respir Crit Care Med.* 2001;163:32–36.
 35. Thoonen, B, Schermer T, van den Boom G, et al. Self-management of asthma in general practice, asthma control and quality of life: a randomised controlled trial. *Thorax.* 2003;58:30–36.
 36. Gallefoss F, Bakke PS. How does patient education and self-management among asthmatics and patients with chronic obstructive pulmonary disease affect medication? *Am J Respir Crit Care Med.* 1999;160:2000–2005.
 37. Gibson PG, Powell H. Written action plans for asthma: an evidence-based review of the key components. *Thorax.* 2004;59:94–99.
 38. Barnes PJ. A single inhaler for asthma? *Am J Respir Crit Care Med.* 2005;171:95–97.
 39. Barnes PJ. Using a combination inhaler (budesonide plus formoterol) as rescue therapy improves asthma control. *BMJ.* 2007;335:513.
 40. Hussain SF. Rapid response to: Barnes PJ. Using a combination inhaler (budesonide plus formoterol) as rescue therapy improves asthma control. *BMJ.* 2007;335:513. <http://www.bmj.com/cgi/eletters/335/7618/513#176161>. Accessed December 30, 2009.
 41. Lipworth BJ. Rapid response to: Barnes PJ. Using a combination inhaler (budesonide plus formoterol) as rescue therapy improves asthma control. *BMJ.* 2007;335:513. <http://www.bmj.com/cgi/eletters/335/7618/513>. Accessed December 30, 2009.
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1. d
2. a
3. c
4. d
5. b