

Safety and Effectiveness of Long-Acting Inhaled β -Agonist Bronchodilators When Taken with Inhaled Corticosteroids

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Long-acting β -agonists are a pillar of therapy for many patients with asthma because they are the preferred add-on therapy to inhaled corticosteroids. However, a recent meta-analysis documented a substantial increase in severe exacerbations requiring hospital admission and life-threatening asthma exacerbations in patients treated with long-acting β -agonists. A careful evaluation of this meta-analysis raises several concerns about its applicability to current practice. Pivotal trials evaluating the benefit of adding long-acting β -agonists to inhaled corticosteroids were not included. The

authors of the current paper call for physicians to continue their usual practice of using long-acting β -agonists as adjunctive therapy, as well as for an independent meta-analysis of individual patients using inhaled corticosteroids and long-acting β -agonists concomitantly.

Ann Intern Med. 2006;145:692-694.

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Beginning with the first asthma guidelines in 1990 (1), leaders in Canadian respiratory medicine have emphasized anti-inflammatory therapy for asthma with inhaled corticosteroids. This practice has since become the standard of care in Canadian specialist and primary care practices for all patients with more than occasional symptoms (2, 3). The use of long-acting β -agonists without concomitant inhaled corticosteroids has always been strongly discouraged (2), and the wisdom of this approach was confirmed by studies showing worsening of eosinophilic airway inflammation and asthma control when long-acting β -agonists were used with no or insufficient concomitant use of inhaled corticosteroids (4–6). On the basis of strong evidence derived from Cochrane reviews (7, 8) specifically updated or produced for the 2003 Canadian Consensus Statement (3), we endorsed long-acting β -agonists as the preferred add-on therapy to inhaled corticosteroids in line with U.S. guidelines (9).

Recently, several authors have questioned the overall safety of long-acting β -agonists (10–12). Prominent in the meta-analysis by Salpeter and colleagues (12) is the Salmeterol Multicenter Asthma Trial (SMART) (11). This large trial, which included more than 25 000 patients, found no difference between patients randomly assigned to receive salmeterol and those assigned to receive placebo for the primary outcome, respiratory-related deaths or life-threatening experiences. There was, however, an excess in respiratory-related deaths (relative risk, 2.16 [95% CI, 1.06 to 4.41]) and in asthma-related deaths (relative risk, 4.37 [CI, 1.25 to 15.34]) among patients receiving salmeterol. The new information provided by Salpeter and colleagues' meta-analysis concerns an apparent excess risk for severe exacerbations requiring hospitalization (Peto odds ratio [OR], 2.6 [CI, 1.6 to 4.3]) and life-threatening exacerbations requiring intubation and ventilation (OR, 1.8 [CI, 1.1 to 2.9]) (12).

A careful evaluation of Salpeter and colleagues' paper raises several concerns about the applicability of this systematic review to therapy as recommended by current

guidelines. In 12 of 19 studies used in the primary analysis, including SMART, patients were not required to take inhaled corticosteroids during the study period. The subgroup analysis presented by Salpeter and colleagues according to the use of inhaled corticosteroids at baseline does not answer the relevant question of the safety of long-acting β -agonists when used in conjunction with inhaled corticosteroids. For example, in SMART, patients were given a supply of salmeterol each month to take as maintenance medication (11). For the approximately 50% of patients who were taking inhaled corticosteroids at recruitment, there was little incentive to continue with a maintenance medication that was not being provided. Also, Salpeter and colleagues provide scant justification for excluding 51 trials by using a trial length of at least 3 months as one of the inclusion criteria. Although they stated that a minimum of 3 months of therapy is needed to observe adverse events, they analyzed adverse events that occurred in the first 3 months of their included studies.

The results of Salpeter and colleagues' meta-analysis differ sharply from those of 2 Cochrane reviews that examined the risk for severe exacerbations requiring hospital admission in patients receiving long-acting β -agonists in addition to inhaled corticosteroids (7, 8) (Table). One pertained to trials with a placebo control (7), and the other compared the addition of a long-acting β -agonist to an increase in the dose of inhaled corticosteroids (8). In these meta-analyses, an important criterion for the inclusion of a trial was that all patients continued to receive inhaled corticosteroids. An excess of hospital admissions for asthma

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Table. Asthma Hospitalizations and Odds Ratios according to Concurrent Use of Inhaled Corticosteroids

Study, Year (Reference)	Inhaled Corticosteroids	Trials, n	Long-Acting β -Agonist Recipients		Control Recipients		Peto Odds Ratio (95% CI)*
			Asthma Hospitalizations/ Patients, n/n	Rate per 1000	Asthma Hospitalizations/ Patients, n/n	Rate per 1000	
Salpeter et al., 2006 (12)	Inconsistent use	12	53/3083	17	12/2008	6	2.6 (1.6–4.3)
Ni Chroinin et al., 2005 (7)	Same dose in both groups	10	26/2097	12	32/2065	16	0.80 (0.47–1.35)
Greenstone et al., 2005 (8)	Higher dose in control group	13	12/2470	5	15/2207	7	0.70 (0.33–1.5)

* Peto odds ratios were calculated from the Cochrane reviews to provide estimates equivalent to those provided by Salpeter and colleagues.

was not observed in the group randomly assigned to receive a long-acting β -agonist in either meta-analysis (Peto ORs, 0.80 [CI, 0.47 to 1.35] and 0.70 [CI, 0.33 to 1.5], respectively). Furthermore, the OR for hospitalization reported by Salpeter and colleagues of 2.6 and the lower confidence limit of 1.6 are both outside the 95% confidence limits of both Cochrane reviews. Although the 2 Cochrane reviews did not report life-threatening asthma, no between-group differences were found in the risk for serious adverse health events or withdrawals due to adverse health events.

Many pivotal studies of concurrent therapy with inhaled corticosteroids and long-acting β -agonists (13–15), as well as more recent studies of such combinations in a single inhaler (16, 17), were not included in Salpeter and colleagues' analysis because they were not placebo-controlled but compared different maintenance regimens for asthma. Thus, the discordance between the findings of the Cochrane reviews and Salpeter and colleagues' analysis seems to be due to the latter's inclusion of studies in which continued use of inhaled corticosteroids was not required. It is therefore very likely that the excess hospitalization and life-threatening events in patients randomly assigned to receive long-acting β -agonists resulted from the insufficient use of inhaled corticosteroids. The occurrence of such adverse events probably also reflects particularly inadequate therapy in vulnerable populations with poor access to medical care. Although common functional variants of the β_2 -receptor (more common in African-American persons) have been associated with deterioration of asthma when such patients use short-acting β_2 -receptors on a regularly scheduled basis (18), it is unclear whether similar adverse effects are associated with regular use of long-acting β -agonists and whether such effects are clinically significant.

The call to reconsider the use of the most effective add-on therapy to inhaled corticosteroids is not constructive. It would seriously compromise asthma control and increase by 20% the risk for exacerbations requiring systemic steroids in a large proportion of high-risk patients (7). We feel it is critical for the individual-patient data from these trials to be made available. An independent meta-analysis could then be performed to confirm the

safety of long-acting β -agonists when used in conjunction with inhaled corticosteroids.

We also have concerns regarding Glassroth's accompanying editorial (19), which advocates a reversal in current practice. The author suggested that higher doses of an inhaled corticosteroid should be tried before adding a long-acting β -agonist to the maintenance regimen. This recommendation ignores the results of clinical trials that clearly show that symptoms, lung function, and quality of life improve more when patients whose asthma is uncontrolled with low or moderate doses of inhaled corticosteroids receive an add-on long-acting β -agonist than when their dose of inhaled corticosteroids is increased 2-fold or more (8, 17). The greatest benefit from inhaled corticosteroids occurs with low doses (20); higher doses are associated with substantial systemic absorption and a small increase in serious adverse events, such as fractures and cataracts (21, 22).

Hospitalizations and mortality rates have been declining steadily since 1995 in the United States, Canada, and Australia (23–25) despite rapidly increasing use of long-acting β -agonists. This is difficult to reconcile with Salpeter and colleagues' claim that 4000 of the 5000 deaths from asthma each year in the United States are attributable to the use of long-acting β -agonists. If this were the case, the number of deaths from asthma would have doubled in this interval.

In conclusion, at the recent Canadian asthma guideline meeting, we were very comfortable in recommending that long-acting β -agonists remain the first choice as add-on therapy to inhaled corticosteroids for patients whose disease is not adequately controlled with low doses of inhaled corticosteroids. Preferentially, this combination therapy should be provided in a single inhaler to avoid the possibility of treating asthma with a long-acting β -agonist alone.

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Potential Financial Conflicts of Interest: *Consultancies:* P. Ernst (Altana, AstraZeneca, Novartis, Merck, GlaxoSmithKline), A. McIvor (Altana, AstraZeneca, GlaxoSmithKline Canada), F.M. Ducharme (AstraZeneca), L.-P. Boulet (Altana, AstraZeneca, GlaxoSmithKline, Novartis, Merck Frosst), M. FitzGerald (AstraZeneca, GlaxoSmithKline), K.R. Chapman (Altana, AstraZeneca, Biovail, Boehringer-Ingelheim, Genpharm, GlaxoSmithKline, Hoffman-LaRoche, Merck Frosst, Novartis, Pfizer, Schering-Plough, Telacris), T. Bai (GlaxoSmithKline Canada, AstraZeneca Canada); *Honoraria:* P. Ernst (Altana, AstraZeneca, Merck Frosst, Novartis, GlaxoSmithKline), A. McIvor (Altana, AstraZeneca, GlaxoSmithKline Canada), F.M. Ducharme (GlaxoSmithKline), L.-P. Boulet (3M, Altana, AstraZeneca, GlaxoSmithKline, Merck Frosst, Novartis), M. FitzGerald (AstraZeneca, GlaxoSmithKline), K.R. Chapman (3M, Altana, AstraZeneca, Boehringer-Ingelheim, GlaxoSmithKline, Merck Frosst, Novartis, Pfizer, Telacris); *Grants received:* P. Ernst (GlaxoSmithKline), F.M. Ducharme (GlaxoSmithKline), L.-P. Boulet (3M, AllerGen, Altana, Asthmatx, AstraZeneca, Boehringer-Ingelheim, Canadian Institutes of Health Research, Dynavax, Fond de Recherche en Santé du Québec, Genentech, GlaxoSmithKline, Institut de Recherche en Santé et Sécurité au Travail du Québec, IVAX, Merck Frosst, National Institute for Occupational Safety and Health (Centers for Disease Control and Prevention), Novartis, Pfizer, Roche, Québec Asthma and Chronic Obstructive Pulmonary Disease Network (Towards Excellence in Asthma Management), Schering, Topigen), M. FitzGerald, K.R. Chapman (3M, Altana, Amgen, AstraZeneca, Bayer, Boehringer-Ingelheim, GlaxoSmithKline, Hoffman-LaRoche, Merck Frosst, Novartis, Telacris, Theratechnologies).

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