

Adult Asthma Consensus Guidelines Update 2003

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BACKGROUND: Several sets of Canadian guidelines for the diagnosis and management of asthma have been published over the past 15 years. Since the last revision of the 1999 Canadian Asthma Consensus Report, important new studies have highlighted the need to incorporate new information into the asthma guidelines.

OBJECTIVES: To review the literature on adult asthma management published between January 2000 and June 2003; to evaluate the influence of the new evidence on the recommendations made in the 1999 Canadian Asthma Consensus Guidelines and its 2001 update; and to report new recommendations on adult asthma management.

METHODS: Three specific topics for which new evidence affected the previous recommendations were selected for review: initial treatment of asthma, add-on therapies in the treatment of asthma

and asthma education. The resultant reviews were discussed in June 2003 at a meeting under the auspices of the Canadian Thoracic Society, and recommendations for adult asthma management were reviewed.

RESULTS: The present report emphasises the importance of the early introduction of inhaled corticosteroids in symptomatic patients with mild asthma; stresses the benefit of adding additional therapy, preferably long-acting beta₂-agonists, to patients incompletely controlled on low doses of inhaled corticosteroids; and documents the essential role of asthma education.

CONCLUSION: The present report generally supports many of the previous recommendations published in the 1999 Canadian Asthma Consensus Report and provides higher levels of evidence for a number of those recommendations.

Key Words: Asthma; Asthma education; Guidelines; Inhaled corticosteroids; Leukotriene receptor antagonists; Long-acting beta₂-agonists

INTRODUCTION

1. Background

The first Canadian guidelines for the diagnosis and management of asthma in Canada were established by a panel of Canadian and international specialists under the leadership of FE Hargreave in 1989 (1). Subsequent meetings in 1995 (2) and 1998 (3), under the auspices of the Canadian Thoracic Society (CTS), led to the revision of the previously published Canadian guidelines. The Canadian Asthma Consensus Report 1999 (3) was widely disseminated and remains a primary reference. A revision of these guidelines followed in 2001 (4) and focused on new information that affected the earlier recommendations. Since this last revision, important new

studies highlight the need to incorporate new information into the asthma guidelines and to address specific issues in childhood asthma not previously addressed comprehensively.

A complete review of the guidelines is complicated and unnecessary in many sections in which new evidence does not significantly affect previous recommendations. Therefore, the Asthma Committee of the CTS agreed to focus on specific issues related to adult asthma, while the Pediatric Consensus Committee of the Canadian Network for Asthma Care (CNAC) focused on specific issues in childhood asthma.

Stakeholders in adult and pediatric asthma met for two days in Montreal, Quebec on June 27 and 28, 2003. The 'adult' group met under the auspices of the CTS, and the 'pediatric'

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TABLE 1
Levels of evidence

Level I	Evidence is based on randomized, controlled trials (or meta-analysis of such trials) of adequate size to ensure a low risk of incorporating false-positive or false-negative results.
Level II	Evidence is based on randomized, controlled trials that are too small to provide Level I evidence. They may show either positive trends that are not statistically significant or no trends and are associated with a high risk of false-negative results.
Level III	Evidence is based on nonrandomized, controlled or cohort studies, case series, case-control studies or cross-sectional studies.
Level IV	Evidence is based on the opinion of respected authorities or expert committees as indicated in published consensus conferences or guidelines.
Level V	Evidence is based on the opinions of those who have written and reviewed the guidelines, based on their experience, their knowledge of the relevant literature and discussion with their peers.

Data from reference 5

TABLE 2
Overall management of asthma

Suspect asthma	Make differential diagnosis
Confirm the diagnosis and assess initial severity	Evaluate symptoms and measure pulmonary function tests (spirometry or peak expiratory flows)
Determine possible triggers and inducers of asthma	Perform a questionnaire, allergy tests or other tests (to assess environment, workplace, etc)
Initiate treatment	Prescribe the medication required to achieve asthma control; treat associated conditions (eg, rhinitis)
Initiate education	Provide basic elements and, if possible, refer patients to an asthma educator
Determine the best results achievable	Check asthma control criteria, including pulmonary function
Determine the minimum medication needed to keep the asthma controlled	Progressively reduce the medication while checking asthma control
Devise an action plan for the management of exacerbations	Provide a written document or ask an asthma educator to do so
Ensure regular follow-up	Regularly check control criteria and pulmonary function

Data from reference 4

group met under the auspices of CNAC. The two groups met separately on the first day to discuss the issues specific to each group and met together on the second day to discuss dissemination and implementation of the asthma guidelines.

The present document deals only with the topics related to the management of adult asthma; the recommendations on childhood asthma will be published separately. The Asthma Committee of the CTS asked a panel of Canadian asthma specialists to perform literature reviews of specific issues related to the management of adult asthma. The experts were chosen for their work and contributions in the field of asthma. The panel systematically reviewed English language studies published between January 1, 2000 and June 2003. During the first day of the June meeting, the whole group reformulated some recommendations based on the literature review to incorporate concerns and suggestions until a consensus on the specific question was achieved.

TABLE 3
Asthma control criteria

Daytime symptoms less than four days per week
Night-time symptoms less than one night per week
Normal physical activity
Mild, infrequent exacerbations
No absenteeism due to asthma
Fewer than four doses per week of a fast-acting beta ₂ -agonist needed*
Forced expiratory volume in 1 s or peak expiratory flow at 90% of their personal best or greater
Diurnal variability in peak expiratory flow of less than 10% to 15%

Data from reference 4. *Apart from one dose/day before exercise

The group based its recommendations on a critical review of the literature and assigned a level to each based on the strength of the supporting evidence (Table 1) (5). The document was subsequently circulated to the whole group and revised according to the group's comments and consensus.

2. Definition of asthma

The definition of asthma is descriptive and has not changed since the last guidelines (3). Asthma is characterized by paroxysmal or persistent symptoms such as dyspnea, chest tightness, wheezing, sputum production and cough, associated with variable airflow limitation and airway hyper-responsiveness to endogenous or exogenous stimuli. Inflammation and its resultant effects on airway structure are considered to be the main mechanisms leading to the development and maintenance of asthma.

This 1999 definition remains valid. Airway inflammation is the primary hallmark of asthma, and better understanding of the underlying pathophysiological mechanisms is important in improving treatment. Indeed, the development of molecules directly targeting specific components of the immune system, such as immunoglobulin E, are the result of this improved understanding and may herald the future for asthma treatment (6).

3. General management of asthma

Optimal management of asthma requires adequate evaluation of the patient and thorough evaluation of environmental factors for that patient (Table 2) (3). When evaluating a new patient, a clinician can assess asthma control by reviewing previously published, but still valid, criteria (Table 3) (3). It is more difficult to assess asthma severity at this early stage, and assessment may be possible only after the asthma is controlled. However, as recommended in the section on mild asthma, treatment with inhaled corticosteroids (ICSs) should be considered early, even in subjects who report asthma symptoms fewer than three times per week. The dose equivalencies used for ICSs in this document (Table 4) were published in the 1999 Canadian Asthma Guidelines (3).

The present consensus update generally supports many of the previous recommendations and provides higher levels of evidence for some of those recommendations.

A central focus of the previous consensus report (3) was the concept of asthma management as a continuum. That management continuum has been modified slightly to reflect the new recommendations presented here (Figure 1).

TABLE 4
Proposed dose equivalencies for inhaled corticosteroids

Product	Daily dose (µg/day)		
	Low	Medium	High
BDP pMDI and spacer	≤500	501-1000	>1000
BUD Turbuhaler*	≤400	401-800	>800
FP pMDI and spacer	≤250	251-500	>500
FP Diskus†	≤250	251-500	>500
BDP pMDI (HFA)‡	≤250	251-500	>500
BUD wet nebulization§	≤1000	1001-2000	>2000

*Budesonide (BUD) Turbuhaler (AstraZeneca Inc, Canada); †Fluticasone propionate (FP) Diskus (GlaxoSmithKline Canada Inc, Canada); ‡In solution with alcohol (QVAR, 3M Pharmaceuticals, Canada) – other hydrofluoralkane (HFA) (propellant) inhalers may provide dose equivalencies similar to BDP delivered with a traditional pressurized metered-dose inhaler (pMDI); §Budesonide solution for wet nebulization (AstraZeneca Inc, Canada). BDP Beclomethasone dipropionate

4. Medications

New therapies targeting the immune system are under investigation for the treatment of asthma. Omalizumab, an anti-immunoglobulin E antibody, has received Food and Drug Administration approval for use in the United States, but is not yet available in Canada (6). The present document focuses on currently available medications in Canada, including ICSs, short- and long-acting beta₂-agonists (LABAs), leukotriene receptor antagonists (LTRAs) and theophylline. Usually, poor asthma control is not a result of ineffectiveness of the medication, but of suboptimal use of that medication, inattention to aggravating factors, poor inhaler technique, poor environmental control or a lack of continuity of care.

5. Dissemination and implementation of the guidelines

The dissemination and implementation of these guidelines are critical for improvement of the management of asthma. An implementation committee comprising representatives of various organizations involved in the field of asthma, as well as representatives from the pharmaceutical industry, will be charged to disseminate and implement the content of these guidelines concomitantly with the pediatric asthma guidelines.

6. Conclusions

The recommendations in this document should be considered to be a guide for asthma management based on currently available evidence. However, each patient with asthma needs to be evaluated individually and objectively with respect to specific outcomes, including symptoms, lung function and occurrence of adverse events. Asthma control and maintenance therapy should be assessed at each visit. Any alteration in medication therapy should be considered a trial and effectiveness re-evaluated after a reasonable period of time.

Additional tools that are currently under investigation, such as induced sputum (7) or exhaled nitric oxide (8), may help to characterize better the level of airway inflammation and improve the management of asthma.

THE ROLE OF ICSs IN THE INITIAL MANAGEMENT OF ASTHMA

1. Background

The inflammatory nature of asthma and the importance of anti-inflammatory therapy is well established in all asthma

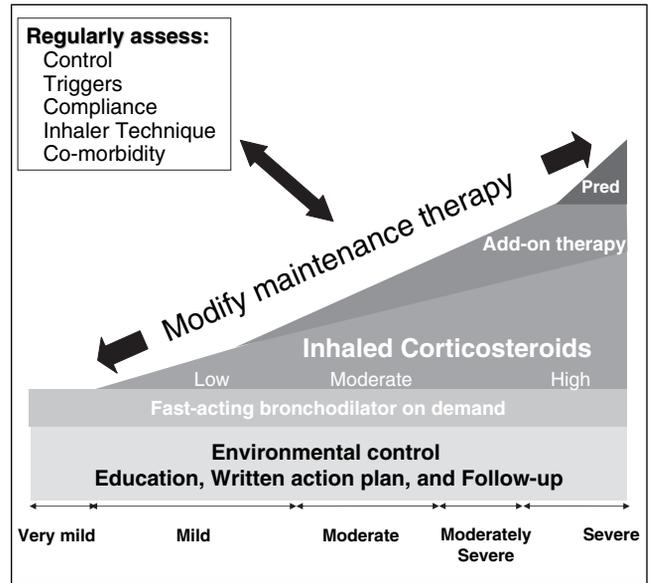


Figure 1) Continuum of asthma management. Very mild asthma is treated with short-acting beta₂-agonists, taken as needed. Inhaled corticosteroids (ICSs) may be introduced as the initial maintenance treatment for asthma, even in subjects who report asthma symptoms less than three times per week. For patients who cannot or will not use ICSs, leukotriene receptor antagonists are an alternative, although they are less effective than low doses of ICSs. If asthma is not adequately controlled by low doses of ICSs, additional therapy should be considered. Addition of long-acting beta₂-agonists should be considered as the first option. As an alternative, addition of leukotriene receptor antagonists or increasing ICSs to a moderate dose of may be considered. Theophylline may be considered as a third therapeutic option. Severe asthma may require additional treatment with prednisone (Pred). Asthma control should be assessed at each visit, and maintenance therapy should be altered if necessary. Any alteration in medication therapy should be considered a trial, and effectiveness should be re-evaluated after a reasonable period of time. After achieving full control, the medication should be reduced to the minimum necessary to maintain control

guidelines (3,9,10). Based on a series of studies in patients who remain poorly controlled despite ICSs, the addition of a LABA has been found to be better than doubling the dose of ICS (11,12). Three major questions remain:

1. What is the optimal time to start ICSs in mild asthma?
2. Which patients may benefit from the initiation of combination therapy instead of ICSs alone?
3. What are the relative merits of the use of ICSs versus LTRAs in mild asthma?

We reviewed the evidence supporting the role of ICSs in mild asthma and critically evaluated the evidence relating to the three questions. This brief systematic review was limited to studies published since 2000. We also requested information about any unpublished papers or data on file within the last three years from all companies who market the relevant drugs.

2. ICSs in mild asthma

There are many studies on the role of ICSs in mild to moderate asthma. Before the period of our review, we identified two

systematic reviews (13,14). One (13) identified 52 studies including 3459 subjects. Beclomethasone showed significant improvements in forced expiratory volume in 1 s (FEV_1) (weighted mean difference 340 mL, 95% CI 190 to 500 mL), FEV_1 (% predicted) (weighted mean difference 6%, 95% CI 0.4% to 11.5%) and morning peak expiratory flow (PEF) (weighted mean difference 50 L/min, 95% CI 8 to 92 L/min) in all studies compared with placebo. In addition to a reduction in the use of short-acting beta₂-agonists, subjects who used ICSs were less likely to have been withdrawn because of an asthma exacerbation (risk ratio [RR] 0.54, 95% CI 0.15 to 0.43) than those on placebo. Additional systematic reviews (13-16) have confirmed the primary role of various ICSs in chronic asthma and have generally shown minimal benefit to increasing ICSs above low doses for patients with mild asthma. The overall interpretation from these studies is that ICSs provide the optimal intervention for patients with mild persistent asthma.

3. Early use of ICSs in mild asthma

Despite the weight of evidence, the rationale for the early use of ICSs in mild, persistent asthma has been unclear and has not always convinced physicians to begin treatment with ICSs. In a large, prospective study designed to address this issue – the START study (17) – 7241 patients were randomly assigned to inhaled budesonide (adult patients, 400 µg daily; children, 200 µg daily) or placebo. Patients had a baseline FEV_1 of 86.6%, with a postbronchodilator value of 96.2%. More than 91% of the patients had symptoms on one or more days in the two weeks before assignment and had not previously been treated with ICSs. The early use of ICSs was associated with better control of symptoms but, most importantly, a significant 44% reduction in severe exacerbations of asthma (RR 0.56, 95% CI 0.45 to 0.71, $P < 0.0001$). The patients also had an improved FEV_1 compared with baseline (1.48% after one year, $P < 0.0001$; 0.88% after three years, $P < 0.0001$). Patients assigned to the treatment group were less likely to need additional anti-inflammatory therapy.

4. ICSs versus combination therapy in mild asthma

Combining a LABA and ICSs has been well established in the management of moderate to severe asthma (18). Less clear-cut is the role of combination therapy in mild to moderate asthma. Few studies have addressed this issue directly. In one study (19), 698 patients (group A) were randomly assigned to receive a low dose ICS (100 µg budesonide twice daily) and a LABA (6 µg formoterol twice daily), an ICS alone (100 µg budesonide twice daily) or placebo. The addition of 6 µg of formoterol to the ICS resulted in improved lung function, but no additional benefit was found when compared with budesonide alone (100 µg twice daily). Compared with placebo, even in this population of patients with mild asthma, the addition of an ICS resulted in a 68% reduction in severe exacerbations. Of 1272 patients treated previously with ICSs – group B of the same study (19) – who had slightly worse lung function (mean FEV_1 per cent predicted value 86% compared with 90%), the addition of formoterol gave additional benefit compared with placebo and, more importantly, compared with doubling of the dose of the ICS.

A small, open, nonrandomized, before and after study of salmeterol and fluticasone evaluated 127 patients for four weeks with ‘mild to moderate’ asthma. Subjects had a mean FEV_1 of 2.68 ± 0.7 L (82.2% predicted) at baseline (20). There was a significant improvement in asthma control in these patients, but the design of the study – small, open and nonrandomized – precludes using the study to make treatment recommendations.

5. ICSs versus LTRAs in mild asthma

As outlined above, ICSs have usually been the initial treatment recommended for mild asthma. An alternative therapy is the use of an LTRA. A recent systematic review compared the effect of ICSs (400 µg of beclomethasone or equivalent) with LTRAs in mild asthma (21). The author identified 13 trials (all of adults except for one study). Patients treated with LTRAs were 60% more likely to suffer an asthma exacerbation that required a course of oral prednisone than patients using ICSs (RR 1.6, 95% CI 1.2 to 2.2). In addition, patients using ICSs had better symptom control and lung function. Patients allocated to treatment with an LTRA were much more likely to be withdrawn from the studies because of poor asthma control (RR 2.5, 95% CI 1.8 to 3.5).

6. Other publications

Our literature search identified 26 other papers (22-47) published in the past three years. Most of these papers were excluded because they had been integrated, in many instances, into recent systematic reviews or they included studies addressing the relative benefits of combination therapy with LABAs and ICSs rather than our primary question, which addressed the early use of ICSs. We also excluded studies if patients were already taking ICSs or if the studies did not include a placebo arm.

7. Recommendations

These recommendations are based on the following definition of mild asthma: intermittent symptoms of asthma, requiring a short- or fast-acting beta₂-agonist at least twice weekly to control symptoms, with an FEV_1 greater than 85% predicted.

1. ICSs should be introduced early as the initial maintenance treatment for symptomatic asthma (Level I evidence).
2. There is insufficient evidence of additional benefit for the initial use of combination therapy in those with mild, symptomatic asthma who have not previously been treated with ICSs (Level I evidence).
3. For patients who cannot or will not use ICSs, LTRAs are an alternative (Level I evidence). However, LTRAs as monotherapy are less effective than low doses of ICSs (Level I evidence).
4. Doses of ICSs recommended in mild asthma are safe (Level III evidence).

8. Suggestions for future research

1. What is the minimal effective dose of ICSs in the treatment of asthma?
2. Can the regular use of ICSs modify the natural history of asthma?
3. Can the monitoring of airway inflammation improve the management of asthma?

- In mild asthma, a significant proportion of patients experience severe exacerbations. The optimal strategy for the prevention of such exacerbations progressing from an early increase in symptoms to a severe asthma exacerbation needs to be defined.

9. Implementation strategies

The key message for family physicians is that we have excellent evidence supporting the early introduction of ICSs in mild asthma. There is no evidence currently supporting the use of combination therapy as first-line treatment for mild asthma as defined previously. Physician and patient education should focus on the recent clinical research that has confirmed the role for the early introduction of ICSs in asthma. Patient education needs to focus on the benefits to the patient and provide reassurance about the safety of ICSs in the doses required to control mild asthma.

ADD-ON THERAPIES IN THE TREATMENT OF ASTHMA

1. Introduction

While ICSs remain the cornerstone of controller therapy for asthma, at least three different classes of medications have been identified as useful add-on therapies in patients not adequately controlled with ICSs: inhaled LABAs (11), oral LTRAs (48) and oral theophylline (49). Each has been shown to improve asthma control or allow for a reduction in the dose of ICS.

We sought to evaluate and compare each medication's efficacy when added to treatment with ICSs, as well as its corticosteroid-sparing effect.

A systematic review of trials published in English since the last asthma guideline update, between January 1, 2000 and June 2003, was performed using PubMed. The key words used were "advair", "antileukotrienes", "formoterol", "long-acting beta₂-agonists", "montelukast", "salmeterol", "seretide", "serevent", "oxeze", "oxis", "ymbicort", "theophylline" and "zafirlukast". GlaxoSmithKline, AstraZeneca and Merck Frosst were contacted to obtain the latest unpublished studies involving their products. We also had access to the Cochrane Library.

Predictably, most studies were industry sponsored. Interpretation of these studies required consideration of possible biases in study design, interpretation or publication. Furthermore, an old and inexpensive drug such as theophylline may have been disadvantaged, because it was unlikely to receive any corporate sponsorship for expensive, large studies of add-on therapy; indeed, little on this drug has been published.

2. LABAs

For several years, LABAs have been established as an effective and safe medication, when used with ICSs, for providing good control of asthma in patients not optimally controlled on a moderate-dose ICS (12). Their use as monotherapy has been assessed (50,51). Recent studies investigated the efficacy of the combination of a LABA with a low dose of ICS in comparison with a higher dose of ICS alone; others evaluated the corticosteroid-sparing effect of the addition of a LABA.

2.1. LABAs as monotherapy for asthma treatment

Salmeterol monotherapy does not provide satisfactory control

of asthma. A randomized, double-blind, placebo controlled, parallel-group study compared triamcinolone (400 µg twice daily) with salmeterol (42 µg twice daily) (50). Despite reasonable control of symptoms and lung function, treatment failure and asthma exacerbations occurred more often in the salmeterol-treated group. A study evaluating the corticosteroid-sparing effect of LABAs noted a large increase in asthma exacerbations (46.3% of patients) after complete elimination of triamcinolone compared with subjects taking both triamcinolone (400 µg twice daily) and salmeterol (13.7% of patients) (51). This has recently been confirmed with the interim analysis of the recently discontinued SMART study, which demonstrated that salmeterol was associated with a significantly higher prevalence of adverse events, including death, than a placebo in the approximately 50% of 26,000 subjects who were not on ICSs (52).

2.2. LABAs versus placebo as add-on therapy to ICSs

Several pivotal studies in adults have clearly demonstrated the superiority of adding a LABA to moderate doses of an ICS compared with doubling the dose of an ICS to improve asthma control (11,12,18,53). More recently, Zetterstrom et al (54) compared combination inhaler budesonide (200 µg) and formoterol (6 µg) with the two inhalers separately and with budesonide (200 µg, two puffs twice daily) alone in 362 subjects. Both combinations were superior to the ICS alone in symptoms, lung function and asthma control. D'Urzo et al (55) compared salmeterol with placebo as add-on therapy in general practice settings in 712 subjects who had asthma and were taking ICSs. They found improvements in symptoms and expiratory flow rates, but no difference in exacerbation rates.

2.3. LABAs as add-on therapy to low-dose ICSs versus doubled doses of ICSs

Heyneman et al (56) reviewed four clinical trials that compared salmeterol and low-dose fluticasone in combination with fluticasone alone. Only one of these studies was placebo controlled. This review included the study by Matz et al (39), which itself is a combination of two studies. Three of these four studies found that the combination of salmeterol 50 µg and fluticasone 100 µg was superior, in most aspects, to fluticasone (250 µg twice daily) alone. The exacerbation rate was lower with the combination of salmeterol and fluticasone in only one study (39). Only one study compared low- to moderate-dose fluticasone (100 to 250 µg twice daily) plus salmeterol with moderate- to high-dose fluticasone (250 to 500 µg twice daily) (42). In this study, the combination therapy provided marginal superiority to monotherapy with an ICS (42). The authors concluded that the combination of salmeterol and low-dose fluticasone is superior to monotherapy with moderate-dose fluticasone. In the post hoc combination of two trials, Matz et al (39) used these large data sets (925 subjects) to demonstrate a decreased exacerbation rate, as had been shown in the FACET study (11), with fluticasone 100 µg and salmeterol 50 µg twice daily compared with fluticasone (250 µg twice daily). Indeed, 41 patients (8.8%) experienced 47 exacerbations with the addition of salmeterol compared with the 63 patients (13.8%) who experienced 75 exacerbations in the group receiving an increased dose of fluticasone (P=0.017).

2.4. LABAs versus placebo as add-on therapy to tapered doses of ICSs

A LABA may be used in addition to an ICS to reduce the ICS dose. Several studies assessed the corticosteroid-sparing effect of a LABA. Lemanske et al (51) studied salmeterol (50 µg twice daily) in addition to triamcinolone (400 µg twice daily) in 154 subjects; one-half of this group was assigned to a 50% reduction in triamcinolone, followed by complete reduction. There was a small (n=21) placebo control group. The primary end point was 'treatment failure', which was three-fold, but not significantly greater, after a 50% reduction in triamcinolone dose at eight weeks, and which was highly significantly greater (46% versus 14%) after complete elimination of triamcinolone after an additional eight weeks. The authors concluded that addition of the LABA allowed a 50% reduction in the ICS. Critics of this study argued that in the group in which the dose of ICS was halved, the number of treatment failures might have increased significantly if the duration of study was longer and if the sample size had been increased (57). They also questioned the study's conclusions.

Price et al (43) studied 663 subjects randomly assigned to receive budesonide (400 µg twice daily) with either placebo or formoterol (12 µg twice daily) for four weeks followed by random reassignment of 505 subjects with good asthma control to a reduced dose of budesonide (400 µg once daily) with placebo or formoterol (12 µg twice daily). Formoterol resulted in more rapid achievement of asthma control in the first four weeks of the study. In the subsequent six-month trial, formoterol plus low-dose budesonide was more effective than low-dose budesonide alone in all aspects, including time to first mild asthma exacerbation. However, the exclusion of the subjects who were not well controlled on treatment combining budesonide and formoterol may have introduced a selection bias.

Busse et al (26) studied 760 subjects. During the first run-in period, patients received fluticasone 250 µg twice daily or the equivalent for 10 to 14 days. Controlled patients moved to the second run-in period where they received fluticasone 100 µg twice daily. Only patients who became unstable on fluticasone 100 µg twice daily were eligible to enter the third run-in period during which they were placed on fluticasone 250 µg twice daily. Those regaining asthma control were eligible for randomization. The authors randomly assigned 277 patients to stay with the same treatment, and assigned 281 subjects to receive the combination treatment, including fluticasone (100 µg) and salmeterol (50 µg) twice daily. The proportion of subjects in each group who remained in the study with no evidence of worsening asthma was the same, as was the total number of exacerbations. PEF rates were higher and salbutamol use was lower in the salmeterol group. The authors concluded that the use of salmeterol allowed for a 60% decrease in the fluticasone dose. However, only one dose reduction was performed, and the magnitude of the corticosteroid-sparing effect may have been overestimated in this study. Indeed, a dose of 350 µg of fluticasone instead of 500 µg may have been sufficient to obtain satisfactory control of asthma in the group without a LABA.

Therefore, the use of LABAs seems to allow for a reduction in the dose of ICSs, but additional studies are needed to establish the magnitude of the corticosteroid-sparing effect and its clinical relevance. In any case, an appropriate dose of ICS should be maintained to avoid the occurrence of asthma exacerbations.

3. LTRAs

3.1. LTRAs versus placebo as add-on therapy to ICSs

A recent meta-analysis (58) that pooled the randomized, controlled trials comparing LTRAs with placebo as add-on therapy to ICSs revealed that montelukast caused a small but significant improvement in PEF, as well as a reduction in beta₂-agonist use and eosinophil count. However, the use of montelukast did not decrease the risk of exacerbations compared with placebo. Only when used at higher doses than that approved for use did pranlukast (450 mg twice daily) or zafirlukast (80 mg twice daily) decrease the risk of exacerbations.

Montelukast was compared with placebo in 100 subjects with poorly controlled asthma who were generally on high-dose ICSs, and most were already on one or two add-on therapies (59). In this study, performed to simulate the 'real world' of poorly controlled asthma, the effect of montelukast was no different from that of the placebo. However, strong criticism resulted in pointing out the biases against an LTRA in a group already on extensive therapy (60,61). As has been previously described (62), the two most common reasons for such high medication requirements with suboptimal control are, first, noncompliance with medication, and second, the possibility that some or perhaps even all symptoms could be the result of something other than asthma (61).

A double-blind, randomized, crossover study (63) compared fluticasone (100 µg twice daily) plus placebo with fluticasone (100 µg twice daily) plus montelukast (10 mg daily) in 28 subjects and found no significant difference between the two in symptoms, lung function and inflammatory markers. A double-blind, multicentre study (64) compared the addition of montelukast to placebo in patients with asthma that were poorly controlled on ICSs (400 to 1600 µg daily). The authors found that compared with the control group, the montelukast-treated group had more asthma-free days, less beta₂-agonist use and improved PEF values. Therefore, the addition of montelukast to an ICS seems to provide a small improvement in asthma control in subjects incompletely controlled by ICSs.

3.2. LTRAs as add-on therapy versus doubled doses of ICSs

A recent meta-analysis (58) reported that only two unpublished trials compared zafirlukast as add-on therapy with doubled doses of ICSs. When zafirlukast was used at four times the approved dose, there were no significant differences in the risk of asthma exacerbations, PEF, symptom score and beta₂-agonist use between groups, but the power of the study was insufficient to claim equivalency.

The addition of montelukast (10 mg) to budesonide (800 µg daily) appeared as effective as budesonide (1600 µg daily) in 889 subjects who were symptomatic after a 30-day run-in on

budesonide (800 µg daily) (65). Improvements in PEF, quality of life and blood eosinophil count were similar between the two groups. The effect on exacerbations was also similar; however, to prove equivalency, several thousand patients would be required. Thus, although the addition of an LTRA to a moderate dose of an ICS appears to be as effective as doubling the doses of an ICS, equivalency has not yet been demonstrated.

3.3. LTRAs versus placebo as add-on therapy to tapered doses of ICSs

A meta-analysis (58) that pooled the results of four trials using LTRAs failed to show a greater reduction of the dose of ICSs in well-controlled patients with asthma treated with LTRAs compared with patients treated with placebo. However, it did show a reduction in withdrawal due to poor asthma control in the groups treated with LTRAs.

Montelukast and placebo were compared in 50 subjects who reduced their ICS dose first to 50% and then to 25% for six weeks each (66). Beclomethasone was successfully reduced from 800 µg daily to 400 µg with no significant differences between the placebo and montelukast groups. Subsequent reduction to 200 µg/day resulted in deterioration in lung function in both groups but an increase in night-time symptoms only in the placebo-treated group.

Montelukast and placebo were compared in 191 patients with moderate to severe asthma who were on high doses of an ICS, and showed a reduction in the ICS by 50% (67). At weeks 8 and 16, the dose was titrated again (reduced again by 50%, maintained or increased). There were no significant differences in the ICS dose between the two groups after the dose was tapered. PEF was slightly but significantly higher in the montelukast group after the reduction in the ICS. There were no significant differences between the two groups in daily activity score, night-time sleep score, FEV₁ and vital capacity over the 24-week treatment period. Thus, the addition of LTRAs to ICSs does not result in greater dose reductions of the dose of the ICS, but may provide better asthma control during tapering.

4. Theophylline

There are few new studies on theophylline as add-on therapy to ICSs. One study compared theophylline, zafirlukast and formoterol added to budesonide (400 µg twice daily) over three months in 64 subjects (68). In this small study, the only significant difference was the earlier improvement in lung function and symptoms in the formoterol-treated group; overall, at three months, there was no significant difference between groups.

Another randomized crossover study (30) compared three treatment blocks: beclomethasone (QVAR, 3M Pharmaceuticals, Canada) 100 µg daily alone for two weeks, followed by 400 µg daily for the next two weeks; beclomethasone (QVAR) 100 µg daily followed by 400 µg daily with the addition of zafirlukast (20 mg twice daily); and beclomethasone (QVAR) 100 µg daily followed by 400 µg daily with the addition of theophylline (200 to 300 mg twice daily). The addition of the LTRA improved asthma control. The addition of LTRA, but not theophylline, to a low dose of ICS had greater effects on the provocative dose of methacholine causing a 20% decrease in FEV₁ (methacholine PD₂₀) and

exhaled nitric oxide than did a low dose of ICS. The effects were not evident with a medium dose of ICS.

5. Comparison between LABAs and LTRAs as add-on therapies

Two large studies compared LTRAs with salmeterol: one study compared zafirlukast (20 mg twice daily) with salmeterol (50 µg twice daily) in 429 patients (69); another compared montelukast (10 mg once daily) with salmeterol (50 µg twice daily) in 948 patients (70). Both studies favoured salmeterol in improving lung function and quality of life, and in reducing symptoms and the need for beta₂-agonist rescue therapy. The differences in the study using montelukast were small and of questionable clinical significance (70). Neither study had a placebo control. The results were consistent with a previous study (41) in 447 subjects who were not optimally controlled on low doses of ICS. The twice-daily combination of fluticasone 100 µg and salmeterol 50 µg was superior to a combination of montelukast 10 mg plus twice-daily fluticasone 100 µg in improving pulmonary function, symptoms and the exacerbation rate. Ringdal et al (71) compared combination therapy of fluticasone 100 µg and salmeterol 50 µg (twice daily) with fluticasone (100 µg twice daily) plus montelukast (10 mg once daily) in 725 subjects with moderate asthma. There was a greater improvement in PEF and FEV₁ in the salmeterol group, as well as fewer exacerbations.

Another study (72) compared montelukast (10 mg daily) with salmeterol (50 µg twice daily) added to an ICS in 20 subjects for two weeks. Both groups showed significant improvements in asthma control, but only montelukast produced significant effects on adenosine-monophosphate challenge and blood eosinophils, suggesting an anti-inflammatory effect. However, the dose and the type of ICS varied among the subjects.

In conclusion, the addition of a LABA to an ICS seems to be more effective than the addition of an LTRA in achieving asthma control in subjects not optimally controlled on ICSs alone. Additional studies are needed to confirm the superior anti-inflammatory effect of LTRAs over LABAs.

6. Conclusions and recommendations on the use of add-on therapy in the treatment of asthma

1. LABAs are not recommended as maintenance monotherapy in asthma (Level I evidence).
2. When, after reassessment of compliance, control of environment and diagnosis, patients are not optimally controlled on low doses of ICSs, therapy should be modified by the addition of a LABA (Level I evidence). Alternatively, addition of LTRAs or increasing the ICS to a moderate dose may be considered (Level I evidence). Theophylline may be considered as a third therapeutic option (Level II evidence).

7. Suggestions for future research

1. Long-term studies are needed to evaluate asthma control and remodelling after combined therapies have been used for many years.
2. Additional studies on the steroid-sparing effects of LABAs and LTRAs as add-on therapies to ICSs are needed.

3. Studies of initial treatment comparing combined therapy with moderate to high doses of ICSs alone in patients with asthma and no previous treatment with ICSs are needed to evaluate the potential benefits of combined therapy over ICSs as first-line therapy in moderate asthma.
4. More studies are needed to compare the asthma control and anti-inflammatory effects of LABAs and LTRAs when used as add-on therapies.

ASTHMA EDUCATION IN ADULTS: AN UPDATE

1. Systematic review

We conducted a systematic review of English language studies of asthma education published after the previous update to the 1999 Canadian Asthma Consensus Guidelines had been completed (73). We used key words such as "asthma" and "education" to perform this search on MEDLINE (PubMed). We also reviewed recent published guidelines (9,10) and relevant Cochrane Reviews (74-76).

The main aspects of education included in this review are the role of education in successful asthma management, the impact of education on asthma control, patient monitoring and self-management plans.

2. Background

2.1. The care gap in asthma management and control

Several surveys of management of asthma (77-79) and control in Canada have shown that physicians and patients are unaware of the gap between the goal of asthma management, which is disease control (3), and the degree of disease control achieved. Current management of asthma in Canada has failed to achieve adequate control, as it has in other countries. One reason for this is the insufficient education of patients (78,80). Nevertheless, disease control is considered to be achievable, desirable and the main outcome on which therapy should be based (3,9,10).

Asthma remains poorly controlled, even though a large number of patients have a prescriptions for ICSs (79). Many patients do not adequately understand the role of their medications and how to use them (78,81). This may partly explain the poor compliance with maintenance therapy, such as ICS therapy (82,83). Furthermore, a clinical diagnosis of asthma may not have been applied to many persons receiving asthma medications or who consult for what seems to be acute asthma.

It is also apparent that physicians may not assess asthma control consistently or systematically, and that their patients are not made explicitly aware of the purpose of asthma management or the definition of disease control (77,78). If, as seems to be the case, appropriate medication is being prescribed for patients with asthma, the poor outcome and lack of awareness of this poor outcome can be addressed only by education to change physicians' and patients' behaviours.

2.2. Asthma education: Is it effective and how should it be delivered?

Previous key studies and analyses have demonstrated that proper self-management and education can result in improved asthma outcomes (84,85). However, comparative analyses of asthma education programs are sometimes

difficult because of the different educational methods used, the duration of the program, the nature of the participants and the methods of evaluation. Although asthma education programs have not always been shown to have a measurable outcome of improved asthma control (3), appropriate education designed to change patients' (or physicians') behaviour is the logical approach to encourage compliance with management. It is difficult to improve patient adherence with prescribed medication (83), but this is true for all measures designed to change behaviour and for all chronic diseases. If asthma education programs are to succeed, they must be tailored to the patients' needs, their state of readiness to accept their diagnosis and their role on the management team (86). The difficulty in demonstrating a measurable outcome from patient education and the disagreement between surveys that examine the same material (75,76) indicate that educational programs must be carefully structured, individualized and expertly delivered to be successful.

2.3. Knowledge and behavioural change

Providing knowledge to patients does not translate into a change in behaviour (87-89), although it is probably an important initial step. The most effective elements of asthma education include device (eg, inhaler) training, understanding the differences between reliever and controller medications, and providing a disease-monitoring process and a self-management (action) plan (75,85). Education must be presented by persons with strong content knowledge, training and proven ability to induce behavioural change (90). It is probable that most education provided by physicians is quite limited and falls short of this ideal (91,92). Nevertheless, it is essential that physicians participate in the education of their patients, and reinforce and support the role of the asthma educators.

2.4. Who should be educated?

Generally, education should have the greatest impact on the most severely affected patients, notably those who use emergency departments and those who require admission to the hospital (93-95). This group may also be more susceptible to educational interventions (93-95). In this regard, Côté et al (94) reported on a group of patients recruited during a visit to the emergency department after an asthma exacerbation. In this study, three groups of patients were enrolled: those receiving usual care, those receiving a short educational intervention in the emergency department and those receiving the short educational intervention plus referral to a specialized asthma educator. Only the last group had a significant improvement in asthma outcomes, including a reduction in subsequent visits to the emergency department.

3. Recent evaluations of asthma education programs

Recently, additional studies have supported the importance and relevance of asthma education concerning self-management in the overall management of the condition. Our review is, however, restricted to studies including an adult population.

Yilmaz and Akkaya (96) studied, over three years, an educational intervention using video cassettes in the outpatient clinic, patient brochures, inhalation device technique verification, patient education, patient education seminars given

six times by a chest physician and the availability of a telephone helpline. Fifty-two patients with asthma and significant baseline airway obstruction had been randomly allocated to an educational intervention group (n=25) and a usual care group (n=27). After three years, the educational group showed a significant improvement in the knowledge score on asthma, improved quality of life and asthma severity scores, and a reduction in the frequency of visits to the emergency department. However, there were no differences between the two groups with regard to admissions. There was a trend toward improved daytime and night-time asthma symptom scores in the educational group.

Couturaud et al (97) reported a randomized, controlled, one-year study in 72 patients. One-half received usual care (control), and one-half was offered education consisting of five individual sessions covering the pathophysiology of asthma, the role of medication and side effects, asthma triggers and their avoidance, detection of an asthma flare-up and a self-management plan based on symptoms and peak flow monitoring. Patients who complied with the action plan in the educated group showed a higher number of symptom-free days than the control group, while the symptom-free days overall were similar in both groups at the end of the study. Changes were similar in both groups, as well as quality of life scores. No difference in asthma knowledge was found between the groups. However, self-management ability scores were significantly higher in the educated group at one year.

Osman et al (98) looked at the influence of a brief self-management program on subsequent admissions for asthma in a 12-month, randomized, controlled trial in adult patients. The intervention consisted of 1 h of education supporting a written self-management plan given during hospital admission for acute asthma. The control group received standard care. One month after discharge, the educated group was more likely to report no daytime or night-time symptoms and no activity limitation. Over the one-year follow-up, 17% of the educated patients and 27% of the control group were readmitted. This beneficial effect was significant in those with a first admission, and there was a trend toward significant reduction in those with a previous admission. The educated group was more likely to be prescribed ICSs at discharge and oral glucocorticoids, as well as to have a follow-up; however, after adjustments for these differences, the self-management program was still significantly more beneficial in those with first admissions for asthma than in the control group. This study shows the influence of such initial intervention in patients with acute asthma, particularly in those with a first-time admission for asthma. It also suggests that the educational program was changing medical practice toward better compliance with current asthma guidelines. The authors suggest that this may be the result of the communication between the educator and the physician. They also suggest that we should take the opportunity of patients' admissions to the hospital to educate them on how to better control their asthma.

Put et al (99) evaluated an intervention in patients with mild to moderate asthma who were randomly assigned to an educational program or usual care. The program consisted of a workbook containing information, exercises and homework assignments. Psychoeducation, and behavioural and

cognitive techniques were also introduced during six 1 h individual sessions. Compared with the controls, the program group reported fewer symptoms, better quality of life, reduced negative feelings, increased adherence to the treatment and improvement in cognitive variables. The authors concluded that participation in an individualized program resulted in improvement of asthma morbidity, asthma-related behaviour and knowledge in subjects reporting symptoms and impairment despite adequate medical therapy. However, this study was limited because the period of observation was only three months; ideally, evaluation should be conducted over a longer period.

Thoonen et al (100) compared patients in general practice receiving self-management training with those receiving usual care. The instruction was provided at four educational visits lasting 30 min, 20 min, 10 min and 10 min, respectively. During follow-up over two years, those who had been instructed in self-management had significantly better asthma control and lost fewer activity days. The trained group had improved quality of life scores, which were significant in the domain of emotions. An interesting additional outcome was an overall reduction in the dose of ICSs but an increase in the number of courses of oral glucocorticoids used by the trained group of 110 patients. There were no differences in exacerbation rate or spirometric measures between the two groups. In contrast, Ignacio-Garcia et al (101) followed up their earlier study of the impact of asthma education with self-management programs, and found improvement in exacerbation rates, use of oral glucocorticoids and lung function. These improvements were apparent three years after entry into the study, and were attributed to reinforcement visits at three, six, 12, 24 and 36 months after entry to the study.

4. Environmental control

A subanalysis of a previous trial by Côté et al (102) revealed an improvement in environmental measures and in the quality of life after a structured educational program. However, those measures were effective mostly against house dust mites; compliance with withdrawal of a domestic animal was poor. More studies should address this problem, because it seems quite difficult to change this behaviour.

5. Education of adolescents

Cowie et al (103) reported on 93 patients aged 15 to 20 years who had visited the emergency department for their asthma. They were randomly assigned either to attend an age-specific asthma program, including assessment, education and management by educators, respiratory therapists and physicians, or to have usual care from their regular physicians. After six months, 62 of the patients completed a questionnaire. Participants in both groups showed marked improvement in their asthma control, with a 73% reduction in the rate of visits to the emergency department, and an improvement in disease-specific quality of life. There were no differences between the two groups, but the educated group fared better in the symptom and emotional domains of the quality of life questionnaire. Thus, significant improvements can be achieved, even though management of asthma seems to be difficult in adolescents. However, it was surprising that the educated group was not significantly better than the control group. In both groups, those completing the

study could have been the more compliant patients, and contamination may have occurred in the control group. Because these patients were enrolled when they were unstable, regression to the mean possibly explains the changes, and it may have been interesting to have had a longer follow-up period. For example, in the study by Côté et al (94), the reduction in visits to the emergency department in the educational group was only apparent in the second six-month follow-up period.

In another study directed at adolescents, peers provided the education (104). Changes in quality of life measured with the Juniper instrument were apparent in some domains, as well as in some of the groups of educated children compared with controls. There was an overall improvement in quality of life in the educated children, but a significant difference was apparent only in the activities domain and was driven by girls, while boys showed a significant improvement in emotions, although there was no overall difference in that domain.

6. Health professional and educator training

Unfortunately, studies on the performance and effectiveness of training programs for asthma educators are few, and there have been none since 1999 to our knowledge. In Canada, certified asthma educators complete an accredited training program and a national examination. All patients with moderate or severe asthma, especially those who suffer severe exacerbations, should be referred to an asthma education program operated by trained educators. Programs are listed on the CNAC Web site at <<http://www.cnac.net/english/clinics.html>> and on the Quebec Asthma and COPD Network Web site at <<http://www.rqam.ca>>.

7. Implications for research

More research on optimal asthma education is necessary, particularly in targeted groups such as those with severe asthma, adolescents and the elderly. Asthma education is an important component of asthma guidelines, and its integration into current care should be promoted in guideline implementation programs (105). Various educational programs have been developed, and the essential components that facilitate behavioural change should be further established. An action plan and regular review seem to be essential, but how to optimize the efficacy and cost effectiveness of those programs remains to be validated in specific populations. Application of these interventions should take into account the resources available, as well as socioeconomic and cultural differences.

Previous studies have shown that the effects of such programs vary with the targeted population. For example, the effects are more pronounced in patients with high asthma-related morbidity, and probably depend on the type of intervention, training of educators, articulation of various interventions, methods of analysis and duration of study. The design of studies looking at the effectiveness of educational programs should account for these factors, and such information should be provided in publications. The confounding effect of concomitant glucocorticoid treatment should be addressed, and results should be corrected for this factor, although it is not always easy to distinguish the effect of the medication from the educational intervention.

8. Recommendations on asthma education and monitoring

1. Education is an essential component of asthma therapy and should be offered to all patients. Educational interventions may be of particular benefit at the time of hospitalization or a visit to the emergency department (Level I evidence).
2. All patients should have written plans for self-management that include medication adjustment in response to severity or frequency or symptoms and medication requirements for relief of symptoms (Level I evidence).
3. Patient self-monitoring may be effective using either measurement of PEF or monitoring of asthma symptoms (Level I evidence).
4. Measurement of expiratory flow, preferably by spirometry, should be done regularly (Level III evidence).
5. Monitoring PEF may be useful in some patients, particularly in those who poorly perceive their airflow obstruction (Level III evidence).
6. Optimal management of asthma should include regular medical and educational follow-up (Level I evidence).
7. Asthma control criteria should be assessed at each visit (Level IV evidence).
8. Socioeconomic and cultural factors should be taken into account when designing asthma education programs (Level II evidence).
9. Education programs should include an evaluation process on the performance of the program with regard to its established goals (Level III evidence).

9. Suggestions for future research

1. What is the effect of the certification of educators on asthma education and clinical outcomes?
2. What are the essential components of an asthma education program?
3. How does one identify high-risk patients for whom education should be emphasized?
4. What is the best way to assess compliance with asthma treatment?
5. How should asthma education be integrated effectively into medical practice?

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