REVIEW SERIES

Asthma exacerbations · 4: Prevention

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Asthma exacerbations are common. They account for a significant morbidity and contribute a disproportionate amount to the cost of asthma management. The optimal strategies for the prevention of asthma exacerbations include the early introduction of anti-inflammatory treatment—most commonly, low dose inhaled corticosteroids. This should be coupled with a structured education programme which has a written action plan as an integral component. Where patients continue to be poorly controlled, the addition of a long acting β agonist should be considered. The latter should not be used as monotherapy and should always be used with inhaled corticosteroids. Atopic patients with a history of repeated exacerbations, especially if they are steroid dependent and with a raised IgE, may be considered as potential candidates for omalizumab. In the early stages of an asthma exacerbation, doubling the dose of inhaled corticosteroids has been shown to be ineffective. The ideal strategy for the management of worsening asthma in patients on combination treatment, especially salmeterol and fluticasone, is uncertain. There is an emerging body of evidence for strategies on how to prevent progression to an exacerbation in patients taking a combination of budesonide and formoterol.

In recent years the importance of asthma exacerbations has been increasingly recognised.[1] It has also become apparent that severe asthma exacerbations can occur in patients with mild disease.[2] Overall, acute asthma episodes—especially hospital admissions—account for disproportionate health care costs compared with the management of stable asthma.[3] Although the management strategy for more severe asthma exacerbations is well recognised[4 5] and usually includes regular bronchodilators, systemic corticosteroids and oxygen therapy, the management of patients in the early stage of asthma exacerbations is less well defined. An additional challenge is that, as asthma control is achieved in more patients with combination therapy (an inhaled corticosteroid (ICS) and a long acting β agonist (LABA)), the correct strategy for the prevention and management of asthma exacerbations in such patients is also unclear.

In this review we will outline our current understanding of the optimal strategies using maintenance therapy to prevent exacerbations and, in particular, focus on strategies for the management of patients at an early stage in asthma exacerbations. We will also review recent data on the optimal strategy for preventing exacerbations in patients on combination therapy. We will not address in detail the pathogenesis of asthma exacerbations or the management of fully developed exacerbations which are covered in accompanying articles in this series.[6 7] The review will focus on the literature on adult asthma.

Asthma exacerbations consist of a sustained, often progressive, deterioration in asthma symptoms and airflow obstruction that occurs over hours to days and can last for days to weeks. These attacks generally allow time for intervention, although a few patients have a rapid onset of an exacerbation.[8] They should be differentiated from periods of poor asthma control.[9 10] Airway inflammation is a consistent feature of these exacerbations where there is evidence of vascular leakage (increased albumin), inflammatory cell infiltration and activation, airway smooth muscle contraction, activation and desquamation of bronchial epithelial cells, and mucus hypersecretion with mucus plug formation. Well characterised triggers of asthma exacerbations include respiratory virus infections, allergen exposure (both occupational and domestic), and respiratory irritants.

MAINTENANCE TREATMENT

Inhaled corticosteroids (ICS)

The pivotal role of inflammation in asthma has led to the early use of anti-inflammatory drugs. Most asthma guidelines identify ICS as the optimal initial treatment for asthma.[11–13] The threshold for the use of ICS has become progressively lower, and a number of systematic reviews have confirmed not only the benefits associated with the use of ICS for symptom control in chronic asthma, but have also shown a reduction in asthma exacerbations. The largest prospective study of ICS in mild asthma showed not only the benefits of ICS in the control of mild disease but also a significant reduction in severe asthma exacerbations.[2] In this study, 7241 patients were randomised to receive budesonide 400 μg or 200 μg (depending on age) versus placebo. There were 198 severe exacerbations in the placebo arm and 117 in the active treatment arm (hazard ratio 0.56, 95% CI 0.45 to 0.71, $p<0.0001$).

A recent study has synthesised the data on the role of ICS and other pharmacological

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Abbreviations: FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long acting β agonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; PEF, peak expiratory flow

interventions in preventing asthma exacerbations and found an overall relative risk (RR) of 0.46 (95% CI 0.34 to 0.62), p<0.001, in subjects treated with ICS compared with placebo.[14] Sin and colleagues found the maximum benefit was greatest in shorter studies (12 weeks duration), with no differences evident when the severity of asthma was evaluated based on forced expiratory volume in 1 second (FEV_1) or on the size of the individual studies. In a further analysis the authors found that a higher dose of ICS was associated with a lower rate of asthma exacerbations (RR 0.77, 95% CI 0.67 to 0.89).

A recent study has also shown that, once control has been achieved, the dose of ICS can be reduced without loss of control and is not associated with an increase in asthma exacerbations.[15] In support of this study, a systematic review has shown that overall parameters of asthma control—apart from airway hyperresponsiveness—are no better in subjects started on high dose ICS compared with low to moderate dose ICS.[16]

In preventing asthma exacerbations, there is no convincing evidence to support starting with combination therapy (that is, an ICS and a LABA) compared with ICS alone in steroid naïve patients. This has been shown in individual studies[12] as well as in a recent systematic review.[17] In the OPTIMA (group A) trial, 698 patients were assigned to either 100 μg budesonide alone or with formoterol 4.5 μg.[18] Budesonide alone reduced the risk of severe exacerbations by 60% and poorly controlled days by 48%. The addition of formoterol provided no benefit in terms of exacerbations, but its use was associated with better lung function. In the systematic review,[17] 18 studies met the inclusion criteria (1061 patients) but only nine had sufficient detail in terms of outcomes that allowed them to be combined. The LABA used was formoterol in two studies and salmeterol in seven. A LABA was added to a dose of 800 μg beclometasone or equivalent in three trials and 400 μg per day in the remaining six. The use of a combination inhaler was not associated with a reduction in risk for the need for a course of oral corticosteroids (RR 1.2, 95% CI 0.8 to 1.9).

The impact of current cigarette smoking and its potential for reducing the efficacy of ICS should be considered in evaluating the effect of this intervention on asthma control in general, and a reduction in asthma exacerbations in particular.[19]

Comparison between ICS and leukotriene receptor antagonists (LTRAs)

National and international guidelines have generally recommended that ICS should be the initial anti-inflammatory treatment in asthma and that leukotriene receptor antagonists (LTRAs) should be reserved for those who ''will not or cannot take'' ICS. A recent systematic review has shown that, compared with LTRAs, ICS are associated with a lower rate of asthma exacerbations.[20] This review, which comprised 13 studies in which patients with mild asthma treated with LTRAs were compared with those treated with low dose ICS (400 μg beclometasone or equivalent), found that patients on LTRAs were 60% more likely to suffer an asthma exacerbation (RR 1.6, 95% CI 1.8 to 3.5).[20] A further systematic review has shown that the addition of montelukast compared with placebo to maintenance ICS was associated with some improvement in asthma control parameters but had no effect on exacerbations. In contrast, when leukotriene modifiers were compared with placebo, there was a significant reduction in asthma exacerbations (RR 0.59, 95% CI 0.49 to 0.71).[14]

Effect of LABA in reducing asthma exacerbations

The initial recognition of the importance of ICS in achieving asthma control and reducing the inflammatory markers led to the concept of titrating the dose of ICS ever higher as patients remained symptomatic. In a landmark study, Greening *et al*[21] showed that doubling the dose of beclomethasone was less effective than the addition of a LABA (salmeterol) in achieving asthma control. This study did not specifically evaluate asthma exacerbations. In a large study designed to evaluate the risk of asthma exacerbations in patients randomised to receive a combination of a LABA (formoterol) and an ICS (budesonide), no increase was found in asthma exacerbations and, somewhat surprisingly based on the a priori concerns of an increased risk of asthma exacerbations, there was in fact a reduction in exacerbations.[22] A more recent systematic review has evaluated the role of LABA in comparison with short acting β agonists and again found the use of this intervention beneficial in reducing exacerbations (RR 0.75, 95% CI 0.64 to 0.88). When a LABA was added to the treatment of patients who remained symptomatic and in whom the dose of ICS was increased (usually doubled), again the combination treatment was shown to be beneficial in reducing exacerbations (RR 0.75, 95% CI 0.64 to 0.88).[23]

In a further evaluation of the role of ICS and LABA in improving asthma control, the GOAL study[24] followed a rigorous methodology and showed the ability to achieve total asthma control in a significant proportion of patients and, using less strict criteria, well controlled asthma in the majority of patients. A reduction in rates of exacerbation based on historical data was seen, but the intervention was not compared with usual care in terms of an effect on asthma exacerbations. The study confirmed the additive benefit of a LABA and incremental doses of ICS, especially in patients with more severe asthma. The effect was less impressive in milder patients who were steroid naïve, which is consistent with other studies.

A recent systematic review has suggested that LABA may be associated with an increased risk of asthma exacerbations and death.[25] In a response to this systematic review we have argued that the results of the review are floored, especially as it only looked at placebo controlled trials and half the patients were on mono therapy with a LABA, which is not recommended practice.[26]

In keep with this response, has been recent regulatory advisory concerning the role of LABA in asthma should alert clinicians to the appropriate use of this class of drug and, in particular, confine its use to treatment in combination with an ICS, ideally in a combination inhaler. If there is a lack of response, which is possible in a small number of patients based on pharmacogenomic studies, an alternative add-on strategy such as an LTRA or, in selected cases, low dose theophylline should be considered.[27]

Initial management of asthma exacerbations

In the past, most asthma guidelines have recommended a doubling of the dose of maintenance ICS early in an asthma exacerbation. This recommendation was based on consensus, but two recent randomised controlled trials have shown no difference in preventing progression of the asthma exacerbation and the need for additional asthma treatment between patients who continued on their maintenance ICS dose and those in whom the dose of ICS was doubled. In one study patients were controlled on a mean maintenance dose of 600 μg budesonide and, at the time of an exacerbation, were randomised either to continue their maintenance dose of budesonide or to double the dose.[28] There was no difference in outcome between the two groups.[17] In a similar study design, Harrison and colleagues randomised 390 patients either to continue on maintenance treatment or to add an additional inhaler equivalent to doubling the dose of ICS. There was no difference between the two groups, with

11% and 12% starting oral prednisone. The risk for starting oral prednisone was 0.95 (95% CI 0.55 to 1.64), p = 0.8.[29]

Other studies in an ambulatory setting[30] and in the emergency department[31] have addressed slightly different questions but provide some support for quadrupling the maintenance dose of ICS. In these studies, this incremental increase was equivalent to 40 mg oral prednisone. Based on these data, in patients experiencing an asthma exacerbation it would seem prudent to at least triple—if not quadruple—the maintenance dose of ICS once symptoms increase and/or peak flow falls. This recommendation needs to be confirmed in prospective controlled trials. If the asthma exacerbation is more severe at presentation or this strategy fails to prevent progression, a short course of oral prednisone is indicated. A further study by Foresi and colleagues has shown that quintupling the dose of budesonide was also associated with a better outcome than baseline treatment with 200 μg budesonide.[32]

Management of exacerbations on combination therapy

With the emergence of combination therapy for maintenance of patients with moderate to severe asthma, the appropriate response to worsening of asthma while on these treatments is important. Although budesonide and fluticasone share similar anti-inflammatory characteristics, there is an important differentiating feature between salmeterol and formoterol which affects how they can be used in the presence of worsening asthma. In general, salmeterol should only be given twice daily at a total dose of 100 μg. In contrast, formoterol can be prescribed on a more frequent basis, and has the potential for quadrupling the lowest recommended daily dose.

A series of studies have addressed the use of varying strategies in worsening asthma in patients using maintenance therapy with a combination inhaler containing formoterol and budesonide. In general, studies in which the usual dose was quadrupled[33–35] have been successful at preventing the need for additional treatment. These studies not only showed better results from a clinical perspective but, in addition, the results were achieved at a much lower overall cost primarily based on the lower doses of treatment required during stable periods of asthma control. In the Canadian study by FitzGerald *et al*,[33] 995 patients were randomised to receive a fixed dose regimen of budesonide and formoterol or a flexible regimen which could be reduced if asthma was well controlled to a single inhalation twice daily of budesonide and formoterol (180 and 4.6 μg, respectively); 93% of patients were able to achieve a dose reduction. Not surprisingly, the adjustable dosing group received a 36% lower dose of budesonide than the fixed dose group (435 μg *v* 682 μg). When an exacerbation occurred, the dose was quadrupled to four inhalations twice daily. Using this strategy, there was a significant reduction in exacerbations (4% *v* 8.9%, p = 0.002) with an odds ratio of 0.43 (95% CI 0.25 to 0.75). The investigators were allowed to increase the dose of ICS in the fixed dose group, and per protocol this was considered an exacerbation but, if these events were excluded, there was still a significant reduction in exacerbations using the adjustable dosing strategy. Similar results were achieved in a European study which followed the same study outline, in contrast to shorter studies or those in which the study intervention was doubling the dose of medication where no benefit was seen. These studies were carried out predominantly in primary care settings and are probably generalisable to the general population of asthma patients. The studies were open label owing to the potential complexity of using multiple inhalers.

A more recent study, the CONCEPT trial, compared a fixed dose of salmeterol with an adjustable dose of budesonide and formoterol.[36] In this randomised controlled trial, daily symptom control was better on the fixed dose strategy and, in addition, there was a significant reduction in asthma exacerbations. An important caveat in this study was that, at some stage, at least 81% of patients in the adjustable dosing arm were on a single inhalation of budesonide and formoterol. This study confirms the benefit of a fixed dose strategy in reducing exacerbations, and indicates that reducing maintenance treatment to one inhalation daily is associated with a failure of adjustable maintenance treatment to reduce exacerbations. This is an important point, as we know that patients tend to reduce treatment—especially corticosteroids (both inhaled and oral)—even following a significant exacerbation.[37]

In a further evolution of this strategy, the combination of formoterol and budesonide has been evaluated as rescue medication in place of the more usually used short acting β agonist. These studies have recently been described using the acronym SMART (Symbicort Maintenance And Rescue Treatment).[38] In the STAY study, 2760 patients were randomised into three different arms: ICS, a combination of budesonide and formoterol both with short acting β_2 agonists as rescue medication, and a combination of budesonide and formoterol both as maintenance and as rescue medication.[39] The latter intervention was associated with a significant prolongation to the time of the first severe exacerbation ($p<0.0001$), giving a 45–47% lower exacerbation risk than budesonide and formoterol plus a short acting β_2 agonist (HR 0.55, 95% CI 0.44 to 0.67) or the comparator ICS arm (HR 0.53, 95% CI 0.43 to 0.65). The experimental arm was also associated with prolonged time to second and third exacerbations as well as improved symptoms, awakenings, and lung function compared with both fixed dosing strategies.

A further study evaluated this strategy in comparison with a combination of salmeterol and fluticasone.[40] In this randomised but non-blinded study, investigators could adjust the levels of maintenance treatment in both arms, with the main difference being the use of a combination of budesonide and formoterol compared with a short acting β agonist.

Table 1 Systematic review of asthma self-management education[47]

Types of interventions studied		No of studies (%)
Information	Transfer of information about asthma and its management	36 (100%)
Self-monitoring	Regular assessment of either symptoms or peak expiratory flow by the participant	33 (92%)
Regular review	Assessment of asthma control, severity and medications by a medical practitioner	24 (67%)
Written action plan	An individualised written plan produced for the purpose of patient self-management of asthma exacerbations. The action plan is characterised by being individualised to the patient's underlying asthma severity and treatment. It also informs the patient when and how to modify medications and when and how to access the medical system in response to worsening asthma	18 (50%)
Optimal self-management intervention	Includes all the above four components	15 (42%)

A total of 2143 patients were randomised and both regimens were associated with improved asthma control, but use of the single inhaler was associated with a significant reduction in the time to the first exacerbation and the total number of exacerbations was also reduced (255 *v* 329).

For patients controlled on a combination of salmeterol and fluticasone in a single inhaler, there are four options: (1) continued observation and use of increased short acting β agonists as rescue medication; (2) addition of extra ICS via an additional corticosteroid inhaler; (3) the provision in patients on a combination of salmeterol and fluticasone 250 µg twice daily of a similar combination of drugs but with the additional device having a fluticasone dose of 500 µg; or (4) a short course of oral prednisone. These recommendations need to be rigorously evaluated in randomised controlled trials to identify the best option. Based on studies outlined above, the incremental increase in the dose of ICS should be equal to a quadrupling of maintenance therapy. However, it should be noted that the use of a combination inhaler might allow for a lower incremental increase in anti-inflammatory treatment.

Guided therapy

Four studies have shown that, if asthma management is adjusted based on various markers of airway inflammation, the outcomes are likely to be better.

Sont and colleagues[41] randomised patients to a strategy of modifying the dose of ICS based on airway hyperresponsiveness compared with clinical parameters. Overall, mild exacerbations were found to be less likely to occur in the experimental arm (a 1.8-fold decrease, p = 0.03). In a study of 74 patients, Green *et al*[42] used sputum eosinophilia as a marker for modifying asthma treatment and compared this with a group of patients managed according to the BTS asthma guidelines and clinical criteria. In the group managed by sputum eosinophilia there was a 63% reduction in exacerbations (95% CI 24 to 100, p = 0.002). In addition, patients in the intervention arm had significantly fewer severe exacerbations (35 *v* 109; p = 0.01). Although the number of patients admitted to hospital was relatively small, the likelihood was much lower in the intervention arm (1 *v* 6; p = 0.047). Both groups received equivalent doses of ICS. In a further study where exhaled nitric oxide was used to modify anti-inflammatory therapy, the dose of ICS was significantly reduced in the intervention arm (370 µg *v* 641 µg) with no change in the frequency of exacerbations.[43]

Jayaram *et al*[44] also evaluated the role of sputum monitoring and its effects on asthma exacerbations. In this study, 117 patients were randomised to management based on clinical criteria and spirometry and compared with treatment guided by sputum eosinophil counts. In the first phase of the study the minimum treatment to maintain control was identified, and subjects were then randomised to the two different treatment arms for a further 2 years of follow up. In the follow up phase there were 126 exacerbations, most of which were in the group managed by clinical criteria (a total of 79). In the intervention arm, time to first exacerbation was longer and the relative risk ratio was lower (by 49%). In addition, the number of exacerbations requiring prednisone was reduced (5 *v* 15). The difference was mainly in eosinophilic exacerbations, with no effect on non-eosinophilic exacerbations which were the most common.

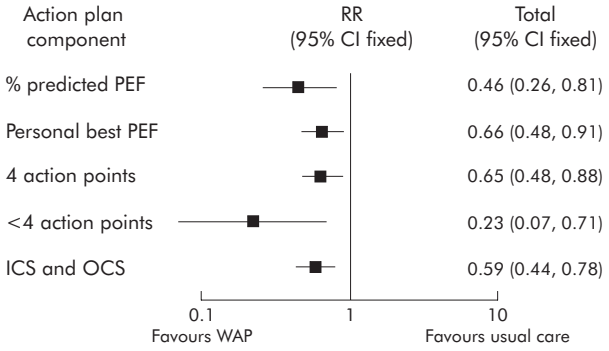

Figure 1 Comparison of the effects of action plan components on hospital admissions for asthma. ICS, inhaled corticosteroid; OCS, oral corticosteroid.

Although the ability to implement these strategies among the general asthma population is currently limited, they do highlight the potential role of these techniques in problematic patients and also help to understand better the heterogeneity of exacerbations and the reasons for an inconsistent response to different interventions in the prevention of exacerbations. A further dose reduction study has also shown the role of sputum eosinophilia in predicting asthma exacerbations.[45]

Table 3 Action plan variations: summary of results[49]

Action plan variation	Result
Action point	
Symptoms *v* PEF triggered	Equivalent
Standard written instruction	Consistently beneficial
Traffic light configuration	Not clearly better than standard instruction
2–3 action points	Consistently beneficial
4 action points	Not clearly better than <4 points
PEF based on personal best PEF	Consistently beneficial
PEF based on % predicted PEF	Not consistently better than usual care
Treatment instruction	
Individualised WAP using ICS and OCS	Consistently beneficial
Individualised WAP using OCS only	Insufficient data to evaluate
Individualised WAP using ICS only	Insufficient data to evaluate

PEF, peak expiratory flow; ICS, inhaled corticosteroid; OCS, oral corticosteroid; WAP, written action plan.

Table 2 Outcomes of asthma self-management education[47]

	Overall effects	Effects of optimal self-management intervention	NNT
Hospital admission	0.64 (0.50 to 0.82)	0.58 (0.43 to 0.77)	21
Emergency visit	0.82 (0.73 to 0.94)	0.78 (0.67 to 0.91)	18
Unscheduled doctor visit	0.68 (0.56 to 0.81)	0.73 (0.58 to 0.91)	24
Days off work	0.79 (0.67 to 0.93)	0.81 (0.65 to 1.01)	12

Results are shown as relative risk (95% CI). All results p<0.05.
NNT, number needed to treat.

Table 4 Asthma education in emergency department attendees[47]

Study	Participants	Recruitment setting	Intervention setting/delivery	Intervention components	Outcome
Brewin[51]	Age >16 years	Hospital	Hospital inpatient/nurse clinician	I, SM	Days off work, nocturnal waking, rescue medications, symptoms, knowledge
Cowie[52]	Adults, adolescents	Post ED discharge	Ambulatory care/nurse clinician	I, SM, RR, AP	Hospitalisations, ED visits
Cote[53]	Age >16 years	Hospital	Ambulatory care/specialist	I, SM, RR, AP	Hospitalisations, ED visits, days off work, knowledge, compliance, OCS
Garrett[58]	Age 2–55 years	ED	Ambulatory care/nurse/ community health worker	I, SM, RR	Hospitalisations, ED visits, days off work, nocturnal waking, PEF variability, symptoms
George[50]	Age 18–45 years	Hospital	Hospital inpatient/asthma educator	I, RR, AP	Hospitalisations, ED visits, length of stay, outpatient visits
Levy[54]	Adults	ED/hospital	Ambulatory care/nurse clinician	I, SM, RR, AP	ED visits, doctor visits, PEF, rescue medications, days off work, symptoms, quality of life, ICS
Mayo[59]	Age >18 years	Hospital	Ambulatory care/ multidisciplinary	I, SM, RR	Hospitalisations, skills, mortality, exacerbations, OCS, ICS
Sommaragua[55]	Adults	Hospital	Hospital inpatient/ multidisciplinary	I, SM, RR, AP	Hospitalisations, ED visits, days off work, exacerbations, respiratory illness survey – psychological factors
Yoon[56]	Age 16–65 years	Hospital	Ambulatory care/asthma educator	I, SM, RR, AP	Hospitalisations, ED visits, days off work, lung function, knowledge, quality of life, knowledge, wheeze, ICS
Zeiger[57]	Age 6–59 years	ED/hospital	Ambulatory care/nurse clinician	I, SM, RR, AP	Hospitalisations, ED visits, nocturnal asthma, ICS, perception of asthma

ED, emergency department; I, information; RR, regular review; SM, self-monitoring; AP, written action plan; ICS, inhaled corticosteroids; OCS, oral corticosteroids; PEF, peak expiratory flow.

Monoclonal anti-IgE

For patients with more severe asthma who have documented atopy and a raised IgE (but below 700 IU), the use of the monoclonal antibody omalizumab was associated with a 45% reduction in exacerbations (RR 0.55, 95% CI 0.45 to 0.66).[14] The high cost of this treatment will probably limit its widespread availability and use, as well as the fact that it has only being shown to be beneficial in a very select population of patients.

ASTHMA EDUCATION

Exacerbations of asthma usually occur gradually over several days to weeks, or on a background of chronic poor asthma control.[9 46] This provides an opportunity for early intervention with corticosteroids and β agonists which act to reverse airflow obstruction and reduce the severity of the exacerbation. A written action plan facilitates the early detection and treatment of an exacerbation and is an essential part of the self-management of exacerbations.[47]

Four main components of asthma education programmes can be identified: information, self-monitoring, regular medical review, and a written action plan (table 1). The effects of an asthma self-management intervention have been evaluated in a systematic review of 36 randomised controlled trials involving 6090 participants with an optimal self-management programme.[47] There was a reduction in the proportion of subjects with an exacerbation requiring admission to hospital, an emergency room visit for asthma, or an unscheduled visit to the doctor (table 2).

Studies have attempted to identify the improvement in asthma that can be attributed to education and to separate this from that attributable to pharmacotherapy.[48] Four randomised controlled trials have been reported in which pharmacotherapy was optimised before administration of an education programme. Pharmacotherapy was optimised by regular medical review and compared with regular medical review combined with an optimal self-management programme where self-adjustment of medication (usually ICS) by the patient was done according to written predetermined criteria. Overall, there was no difference in asthma outcomes between the two forms of asthma management. In particular, exacerbations requiring admission to hospital did not differ between groups. These results indicate that regular medical review is an acceptable alternative to an asthma education programme, providing the medical review includes assessment of severity, optimisation of medication, and instruction on management of exacerbations.

Written action plans

A written asthma action plan is a key component of an asthma education intervention. Written asthma action plans contain four essential components: (1) instruction on when to increase treatment; (2) how to increase treatment; (3) the duration of the treatment increase; and (4) when to cease self-management and seek medical help.[49] The instruction specifying when to increase treatment represents the point at which the action plan is to be activated—that is, the action point. This may be based on symptoms or peak expiratory flow (PEF) values. Self-management using a written action plan based on PEF was found to give similar benefits to self-management using a symptom based written action plan in the six studies which compared these interventions for the proportion of subjects requiring admission to hospital and unscheduled visits to the doctor.[48]

Action points that use PEF can be based on PEF expressed as a percentage of the predicted PEF or as a percentage of the individual's best PEF (personal best). Action points based on personal best PEF were consistently associated with improved outcomes (fig 1). When specifying action points, these can be further subdivided into two levels—for example, 80%, or 60% of the best value (two action points)—or four

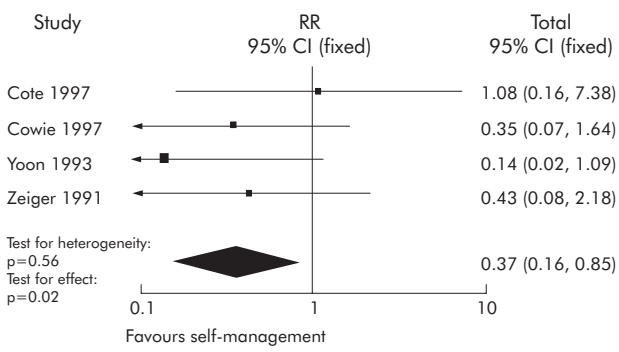

Figure 2 Comparison of the effects of optimal education in the emergency department on hospital admissions.[47] RR, relative risk.

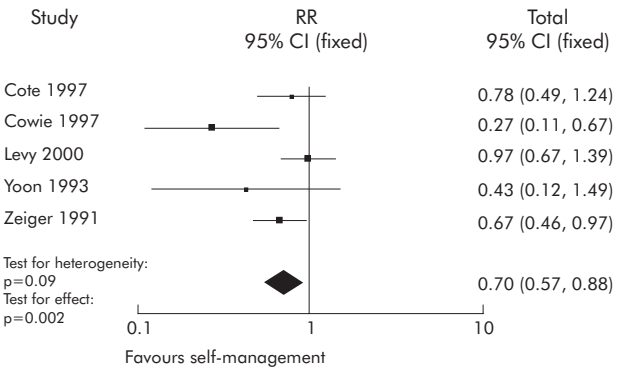

Figure 3 Comparison of the effects of optimal education in the emergency department on subsequent visits to the emergency department.[47] RR, relative risk.

different levels. A comparison of written action plans found that those using two action points had similar results to those using four action points (fig 1).

The instructions regarding treatment showed that action plans recommending increased ICS together with the commencement of oral corticosteroid (OCS) were beneficial (fig 1). Doubling the dose of ICS alone appears to be ineffective, consistent with the results of recent randomised controlled trials that have examined this issue. The recommendations for the use of an action plan are summarised in table 3.

Self-management education following an emergency department visit

Asthma education programmes have targeted emergency department attendees in several randomised trials (table 4).[50–59] The participants have been recruited during or shortly after their visit to the emergency department with acute asthma. Six of these programmes have provided optimal asthma self-management education that has been delivered in an ambulatory care setting after discharge from the emergency department.[52–57] There were significant reductions in subsequent hospital admissions and emergency department visits following these programmes (figs 2 and 3).

Targeting emergency department attendees with acute asthma is an effective management strategy to improve morbidity in asthma. Further randomised controlled trials of self-management interventions during hospital admission in adults have shown reduced morbidity following discharge for the intervention group (daytime wheeze, night disturbance) and readmissions,[60] increased knowledge,[61] outpatient follow up, and reduced subsequent care in the emergency department.[50]

INFLUENZA VACCINATION

Asthma exacerbations are often triggered by viral infections. There has therefore been interest in the role of influenza in the occurrence of asthma exacerbations, but also concern about the possibility that vaccination might precipitate exacerbations. A recent systematic review has provided updated information on this question.[62] The authors included nine trials, four of which were of high quality. A pooled analysis of two trials involving 2306 subjects did not show an increased risk of an asthma exacerbation in the 2 weeks after vaccination (risk difference 0.00, 95% CI −0.02 to 0.2). A more recent study of 696 children with asthma did not show a significant reduction in asthma exacerbations (risk difference 0.01, 95% CI −0.02 to 0.04).

IDENTIFICATION OF PATIENTS AT INCREASED RISK OF EXACERBATIONS

The identification of patients at increased risk of severe asthma exacerbations—most notably, near fatal asthma—has been well described.[63 64] A number of recent studies have evaluated the characteristics of patients with frequent exacerbations. Koga and colleagues compared 32 patients with multiple exacerbations with patients who had at most one exacerbation during the previous year.[65] Patients with multiple exacerbations were more likely to be on higher doses of ICS ($p = 0.0005$), a greater proportion on OCS, need for hospitalisation with an exacerbation ($p = 0.0002$), arrival in an ambulance ($p = 0.008$), concomitant chronic sinusitis ($p = 0.038$), and intolerance to non-steroidal anti-inflammatory drugs ($p = 0.0006$). In a study of similar design, ten Brinke *et al*[66] systematically looked for factors associated with more frequent exacerbations which included severe nasal sinus disease (OR 3.7), gastro-oesophageal reflux (OR 4.9), recurrent respiratory infections (OR 6.9), psychological dysfunction (OR 10.8), and obstructive sleep apnoea (OR 3.4). Severe sinus disease and psychological dysfunction were the only two independently associated factors (adjusted ORs 5.5 and 11.7, respectively).

Attention to these risk factors is likely to be associated with a reduced risk of asthma exacerbations. For example, a recent study has shown that, using clinical criteria for acid reflux, treatment for 24 weeks with 30 mg lansoprazole twice daily versus placebo was not associated with an improved outcome in terms of better asthma control based on symptoms and lung function, although there was a better outcome in the treated group in preventing asthma exacerbations (8% *v* 20.4%, $p = 0.017$) generally as well as in those requiring OCS (4% *v* 13.9% $p = 0.016$).[67] The results are in keeping with a previous systematic review which showed no consistent effect in a general population of asthma patients treated with antireflux therapy.[68] These results are also consistent with our own experience of an increased prevalence of gastro-oesophageal reflux in patients with near fatal asthma.[62] The importance of systematically evaluating patients with frequent exacerbations and difficult to control asthma has recently been stressed.[69]

NON-PHARMACOLOGICAL INTERVENTIONS TO PREVENT EXACERBATIONS

The role of non-pharmacological interventions such as environmental control and homeopathic interventions in asthma management has recently been critically evaluated.[70] There is no convincing evidence that any of these interventions has a part to play in the prevention of asthma exacerbations. It is also difficult to show any effect even on day to day asthma control.

CONCLUSIONS

Asthma exacerbations are common. They are best prevented by the use of optimal first line treatment with anti-inflammatory drugs (most commonly, low dose ICS) in conjunction with a structured asthma education programme. A written action plan should be central to this intervention. Add-on therapy—most commonly a LABA—will not only improve day to day asthma control but has been shown to reduce asthma exacerbations. There is an emerging evidence base for the optimal strategies to use when patients are on a combination of budesonide and formoterol, but further randomised controlled trials are required to address this issue for patients on salmeterol and fluticasone in a combination inhaler. More severe atopic patients may benefit from omalizumab, but the cost effectiveness of this intervention needs to be borne in mind. The ongoing assessment of patients should address issues around adherence to the

treatment plan, especially concerns about chronic medication use and the proper use of inhalers.

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LUNG ALERT

CPAP for OSA is cost effective

▲ Ayas NT, FitzGerald JM, Fleetham JA, *et al*. Cost-effectiveness of continuous positive airway pressure therapy for moderate to severe obstructive sleep apnea/hypopnea. *Arch Intern Med* 2006;**166**:977–84

Untreated obstructive sleep apnoea/hypopnoea (OSAH) is known to be associated with daytime sleepiness, deteriorating health related quality of life (HRQL), hypertension to an individual sufferer, and reduction in daytime performance and an increased incidence of road traffic accidents (RTAs) which has a significant impact on society. Continuous positive airway pressure (CPAP) is known to be an effective treatment of OSAH, which improves symptoms and HRQL. Hitherto, a few studies have found CPAP also to be cost effective at an individual level by incorporating improvement in health status against cost of treatment. This study expands this to a cost benefit analysis by incorporating the benefits to society at large from evaluating the economic impact of a reduction in RTAs by CPAP provision.

Demographic data of driving adults aged 25–54 years newly diagnosed with moderate to severe OSAH were derived from the primary referral centre in British Columbia. The annual probability of an RTA, stratified by severity, was determined using data taken from the National Highway Traffic Safety Administration, as were direct and indirect costs of RTAs. A meta-analysis of eight studies incorporating over 1200 patients was performed to determine the impact of CPAP treatment on the rate of RTAs. The odds ratio was calculated to be 0.15. It was assumed that the RTA rate in treated OSAH was equivalent to that in the general population. The societal perspective of benefit from treatment of OSAH was derived by using the European quality of life questionnaire, which indirectly derives health state values from population surveys using the time-trade off technique. Costs were derived from the 2004 US Medicare fee schedule.

At an individual level, CPAP was found to be more effective but more costly than no CPAP with an incremental cost effectiveness ratio (ICER) of $3354 per quality adjusted life year gained (QALY). When the economic benefit to society of the reduction in RTAs was taken into account, the cost/QALY was reduced by 10-fold.

What this study adds is the significant reduction in cost benefit ratio using just one aspect of societal benefit from treating OSAH. The calculated ICER varies depending both on the measurement tool used and the perspective. The cost benefit analysis may improve further if the potential decrease in cardiovascular morbidity and mortality associated with untreated OSAH is included in the analysis.

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