

## 4 Pharmacological management

The aims of pharmacological management of asthma are the control of symptoms, including nocturnal symptoms and exercise-induced asthma, prevention of exacerbations and the achievement of best possible pulmonary function, with minimal side-effects.

It is not appropriate to define a fixed level of lung function or symptom control which must be achieved, as individual patients will have different goals and may also wish to balance these aims against the potential side-effects or inconvenience of taking the medication necessary to achieve “perfect” control.

In general terms, control of asthma is assessed against these standards:

- minimal symptoms during day and night
- minimal need for reliever medication
- no exacerbations
- no limitation of physical activity
- normal lung function (in practical terms FEV<sub>1</sub> and/or PEF > 80% predicted or best)

2004



Lung function measurements cannot be reliably used to guide asthma management in children under 5 years of age.

A stepwise approach aims to abolish symptoms as soon as possible and to optimise peak flow by starting treatment at the level most likely to achieve this.

Patients should start treatment at the step most appropriate to the initial severity of their asthma.

The aim is to achieve early control and to maintain control by stepping up treatment as necessary and stepping down when control is good (see *Figures 4, 5 and 6 for summaries of stepwise management in adults and children*).

Before initiating a new drug therapy practitioners should check compliance with existing therapies (see *section 11*), inhaler technique (see *section 5*) and eliminate trigger factors (see *section 3*).

2004

2007

All doses of inhaled steroids in this section refer to beclomethasone (BDP) given via CFC-MDIs (metered dose inhaler). Although now almost phased out, this is the device used in most of the evidence-base that supports current asthma management. Adjustment to dose will have to be made for other devices and other corticosteroid molecules.

2007

In this and the following section, each recommendation has been graded and the supporting evidence assessed for adults (> 12 years old), children 5-12 years, and children under 5 years.

1

2

3

**1 Adults**  
**2 Children aged 5-12 years**  
**3 Children under 5 years**



**Recommendation does not apply to this age group.**

#### 4.1 STEP 1: MILD INTERMITTENT ASTHMA

The following medicines act as short-acting bronchodilators:

- inhaled short-acting  $\beta_2$  agonists<sup>157</sup>
- inhaled ipratropium bromide<sup>158</sup>
- $\beta_2$  agonist tablets or syrup<sup>157</sup>
- theophyllines.<sup>157</sup>

> 12 years	5-12 years	< 5 years
1 <sup>++</sup>	1 <sup>+</sup>	4
1 <sup>+</sup>	1 <sup>++</sup>	
1 <sup>++</sup>		
1 <sup>++</sup>		

Short-acting inhaled  $\beta_2$  agonists work more quickly and/or with fewer side-effects than the alternatives.<sup>157</sup>

**A B D** Prescribe an inhaled short-acting  $\beta_2$  agonist as short-term reliever therapy for all patients with symptomatic asthma.

##### 4.1.1 FREQUENCY OF DOSING OF INHALED SHORT-ACTING $\beta_2$ AGONISTS

**2005**

Using short acting  $\beta_2$  agonists as required is at least as good as regular (four times daily) administration.<sup>159,160</sup> Unless individual patients are shown to benefit from regular use of inhaled short-acting  $\beta_2$  agonists then as required use is recommended.

> 12 years	5-12 years	< 5 years
1 <sup>++</sup>	1 <sup>++</sup>	1 <sup>++</sup>
2 <sup>++</sup>	4	4

Using two or more canisters of  $\beta_2$  agonists per month or > 10-12 puffs per day is a marker of poorly controlled asthma.<sup>161</sup>

**B D D** Patients with a high usage of inhaled short-acting  $\beta_2$  agonists should have their asthma management reviewed.

#### 4.2 STEP 2: INTRODUCTION OF REGULAR PREVENTER THERAPY

For steps 2, 3, and 4, treatments have been judged on their ability to improve symptoms, improve lung function, and prevent exacerbations, with an acceptable safety profile. Improvement of quality of life, while important, is the subject of too few studies to be used to make recommendations at present.

##### 4.2.1 INHALED STEROIDS

**2007**

Inhaled steroids are the most effective preventer drug for adults and older children for achieving overall treatment goals.<sup>162-166</sup> There is an increasing body of evidence demonstrating that they are also safe and effective in infants and younger children with asthma.<sup>668-671</sup>

> 12 years	5-12 years	< 5 years
1 <sup>++</sup>	1 <sup>++</sup>	1 <sup>++</sup>

**A A A** Inhaled steroids are the recommended preventer drug for adults and children for achieving overall treatment goals

**2004**

The exact threshold for introduction of inhaled steroids has never been firmly established. Two recent studies have shown benefit from regular use of inhaled steroids in patients with mild asthma.<sup>526,527</sup> Benefit in these studies was seen even with an FEV<sub>1</sub> of 90% predicted.

> 12 years	5-12 years	< 5 years
1 <sup>-</sup>	1 <sup>+</sup>	

**2004**

**2005**

**B C ✓** Inhaled steroids should be considered for patients with any of the following:

- exacerbations of asthma in the last two years
- using inhaled  $\beta_2$  agonists three times a week or more
- symptomatic three times a week or more, or waking one night a week.

Starting dose of inhaled steroids

In mild to moderate asthma, starting at very high doses of inhaled steroids and stepping down confers no benefit.<sup>167</sup>

> 12 years	5-12 years	< 5 years
1 <sup>+</sup>	1 <sup>+</sup>	

- ✓ Start patients at a dose of inhaled steroids appropriate to the severity of disease.
- ✓ In adults, a reasonable starting dose will usually be 400 mcg per day and in children 200 mcg per day. In children under 5 years, higher doses may be required if there are problems in obtaining consistent drug delivery.
- ✓ Titrate the dose of inhaled steroid to the lowest dose at which effective control of asthma is maintained.

#### Frequency of dosing of inhaled steroids

2007

Most current inhaled steroids are slightly more effective when taken twice rather than once daily, but may be used once daily in some patients with milder disease.<sup>157,165,672</sup>

> 12 years	5-12 years	< 5 years
1+	1+	

There is little evidence of benefit for dosage frequency more than twice daily.<sup>165</sup>

2007

A D D

Give inhaled steroids initially twice daily, except ciclesonide which is given once daily.

A D D

Once a day inhaled steroids at the same total daily dose can be considered if good control is established.

#### 4.2.2 SAFETY OF INHALED STEROIDS

The safety of inhaled steroids is of crucial importance and a balance between benefits and risks for each individual needs to be assessed. Account should be taken of other topical steroid therapy when assessing systemic risk. It has been suggested that steroid warning cards should be issued to patients on high dose inhaled steroids, but the benefits and possible disadvantages of such a policy remain to be defined.

##### Adults

There is little evidence that doses below 800 mcg per day cause any short-term detrimental effects apart from the local side-effects of dysphonia and oral candidiasis. However, the possibility of long-term effects on bone has been raised. One recent systematic review reported no effect on bone density at doses up to 1000 mcg per day.<sup>528</sup> The significance of small biochemical changes in adrenocortical function is unknown.

2004

2004

✓

Titrate the dose of inhaled steroid to the lowest dose at which effective control of asthma is maintained.

##### Children

Administration of inhaled steroids at or above 400 mcg a day of BDP or equivalent may be associated with systemic side-effects.<sup>168</sup> These may include growth failure and adrenal suppression. Isolated growth failure is not a reliable indicator of adrenal suppression and monitoring growth cannot be used as a screening test of adrenal function.<sup>571,672</sup> Clinical adrenal insufficiency has been identified in a small number of children who have become acutely unwell at the time of intercurrent illness. Most of these children had been treated with high doses of inhaled corticosteroids. The smallest dose of inhaled steroids compatible with maintaining disease control should be used. At higher doses, add-on agents, for example, long-acting  $\beta_2$  agonists, should be actively considered.

2005

2007

✓

Monitor children's height on a regular basis.

**2007** → The low dose ACTH test is considered to provide a physiological stimulation of adrenal responsiveness but it is not known how useful such a sensitive test is at predicting clinically relevant adrenal insufficiency.<sup>667,673</sup>

The dose or duration of inhaled steroid treatment required to place a child at risk of clinical adrenal insufficiency is unknown but is likely to be at least  $\geq 1000\text{mcg}$  per day of BDP or equivalent. In addition, it is unknown how frequently tests of adrenal function would need to be repeated if a child remained on high dose inhaled corticosteroid.

**2007** →

- Specific written advice about steroid replacement in the event of a severe intercurrent illness should be part of the management plan for children treated with  $\geq 800\text{mcg}$  per day of BDP or equivalent.
- ✓ ■ Any child on this dose should be under the care of a specialist paediatrician for the duration of the treatment.
- Consider the use of a steroid warning card.

**2005** →

- ✓ ■ Consider the possibility of adrenal insufficiency in any child maintained on inhaled steroids presenting with **shock** or a decreased level of consciousness; **serum biochemistry and** blood glucose levels should be checked urgently.
- Consider whether intramuscular (IM) hydrocortisone is required.

**2004** → ✓ **Titrate the dose of inhaled steroid to the lowest dose at which effective control of asthma is maintained.**

#### 4.2.3 COMPARISON OF INHALED STEROIDS

Many studies comparing different inhaled steroids are of inadequate design and have been omitted from further assessment. In view of the clear differences between normal volunteers and asthma patients in the absorption of inhaled steroids, data from normal volunteers have not been taken into account. Only studies in which more than one dose of at least one of the inhaled steroids or both safety and efficacy had been studied together in the same trial were evaluated. Non-blinded studies also had to be considered because of the problems of obtaining competitors' delivery devices. All comparisons used BDP-CFC (chlorofluorocarbons) as the reference.

BDP and budesonide are approximately equivalent in clinical practice, although there may be variations with different delivery devices. There is limited evidence from two open studies of less than ideal design that budesonide via the turbohaler is more clinically effective.<sup>169</sup> However, at present a 1:1 ratio should be assumed when changing between BDP and budesonide.

Fluticasone provides equal clinical activity to BDP and budesonide at half the dosage. The evidence that it causes fewer side-effects at doses with equal clinical effect is limited.

**2004** → **Mometasone is a new inhaled steroid and the relatively limited number of studies suggests it is equivalent to twice the dose of BDP-CFC.<sup>521</sup> The relative safety of mometasone is not fully established.**

**2005** → **Ciclesonide is a new inhaled steroid.** Evidence from clinical trials suggests that it has less systemic activity and local oropharyngeal side effects than conventional inhaled steroids. The clinical benefit of this is not clear as the exact efficacy to safety ratio compared to other inhaled steroids has not been fully established.

**2007** →

4.2.4 SMOKING

**2007** Current and previous cigarette smoking reduces the effect of inhaled steroids which may be overcome with increased doses.<sup>674</sup>

**B** Clinicians should be aware that higher doses of inhaled steroids may be needed in patients who are smokers/ex-smokers.

✓ Patients should be advised that smoking reduces the effectiveness of therapy.

4.2.5 OTHER PREVENTER THERAPIES

**2004** Inhaled steroids are the first choice preventer drug. Long-acting inhaled  $\beta_2$  agonists should not be used without inhaled corticosteroids.<sup>529</sup> Alternative, less effective preventer therapies in

**2005** patients taking short-acting  $\beta_2$  agonists alone are:

- Chromones

**2004** - Sodium cromoglicate is of some benefit in adults<sup>170,675</sup> and is effective in children aged 5-12<sup>572</sup>

**2005** - Nedocromil sodium is also of benefit in adults and children > 5<sup>170,519</sup>

**2007** - There is no clear evidence of benefit with sodium cromoglicate in children aged < 5<sup>573</sup>

- Leukotriene receptor antagonists have some beneficial clinical effect<sup>165 172 666</sup>

- Theophyllines have some beneficial effect<sup>157,164</sup>

- Antihistamines and ketotifen are ineffective.<sup>175</sup>

	> 12 years	5-12 years	< 5 years
1+			
1++		1+	
1++			1++
1+		1+	1+
1++		1++	1++

**2004** ✓ Long-acting inhaled  $\beta_2$  agonists should only be started in patients who are already on inhaled corticosteroids.

**2007** The Medicines and Healthcare products Regulatory Agency (MHRA) has completed a full review of the balance of risks and benefits associated with long-acting beta<sub>2</sub> agonists in the management of asthma and chronic obstructive pulmonary disease (see [www.mhra.gov.uk/home/idcplg?IdcService=SS\\_GET\\_PAGE&ssDocName=CON2030319&ssSourceNodId=1016&ssTargetNodId=221](http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&ssDocName=CON2030319&ssSourceNodId=1016&ssTargetNodId=221))

4.3 STEP 3: ADD-ON THERAPY

**2007** In a proportion of patients asthma may not be adequately controlled at step 2. Before initiating a new drug therapy practitioners should recheck compliance, inhaler technique and eliminate trigger factors. The duration of a trial of add-on therapy will depend on the desired outcome. For instance, preventing nocturnal awakening may require a relatively short trial of treatment (days or weeks), whereas preventing exacerbations of asthma or decreasing steroid tablet use may require a longer trial of therapy (weeks or months). If there is no response to treatment the drug should be discontinued.

4.3.1	CRITERIA FOR INTRODUCTION OF ADD-ON THERAPY	> 12 years	5-12 years	< 5 years
	No exact dose of inhaled steroid can be deemed the correct dose at which to add another therapy. The addition of other treatment options to inhaled steroids has been investigated at doses from 200-1000 mcg in adults and up to 400 mcg in children. <sup>176-179</sup> Many patients will benefit more from add-on therapy than from increasing inhaled steroids above doses as low as 200 mcg/day. Furthermore, at doses of inhaled steroid above 800 mcg/day side-effects become more frequent. An absolute threshold for introduction of add-on therapy in all patients cannot be defined.	1 <sup>++</sup>	1 <sup>+</sup>	

**A** **B**  **Carry out a trial of other treatments before increasing the inhaled steroid dose above 800 mcg/day in adults and 400 mcg/day in children.**

4.3.2	ADD-ON THERAPY	> 12 years	5-12 years	< 5 years
	Options for add-on therapy are summarised in Figure 3.			
	In adult patients taking inhaled steroids at doses of 200-800 mcg/day and in children taking inhaled steroids at a dose of 400 mcg/day the following interventions are of value:			
	<ul style="list-style-type: none"> <li>First choice would be the addition of an inhaled long-acting <math>\beta_2</math> agonist (LABA), which improves lung function and symptoms, and decreases exacerbations.<sup>176,180,181</sup></li> </ul>	1 <sup>++</sup>	1 <sup>++</sup>	

**A** **B**  **The first choice as add-on therapy to inhaled steroids in adults and children (5-12 years) is an inhaled long-acting  $\beta_2$  agonist.**

	If, as may happen, there is no response to inhaled long-acting $\beta_2$ agonist, stop the LABA and increase the dose of inhaled steroid to 800 mcg/day (adults) or 400 mcg/day (children) if not already on this dose. If there is a response to LABA, but control remains poor, continue with the LABA and increase the dose of inhaled steroid to 800 mcg/day (adults) or 400 mcg/day (children 5-12 years). <sup>182</sup>	> 12 years	5-12 years	< 5 years
		4	4	

**D** **D**  **If asthma control remains sub-optimal after the addition of an inhaled long-acting  $\beta_2$  agonist then the dose of inhaled steroids should be increased to 800 mcg/day in adults or 400 mcg/day in children (5-12 years).**

<b>2007</b>	<ul style="list-style-type: none"> <li><b>Leukotriene receptor antagonists</b> may provide improvement in lung function, a decrease in exacerbations, and an improvement in symptoms.<sup>171,183,184</sup></li> <li><b>Theophyllines</b> may improve lung function and symptoms, but side-effects occur more commonly.<sup>177</sup></li> <li><b>Slow release <math>\beta_2</math> agonist tablets</b> may also improve lung function and symptoms, but side-effects occur more commonly.<sup>176</sup></li> </ul>	> 12 years	5-12 years	< 5 years
		1 <sup>++</sup>	1 <sup>++</sup>	1 <sup>+</sup>
		1 <sup>++</sup>	1 <sup>-</sup>	
		1 <sup>++</sup>		

If control is still inadequate after a trial of LABA and after increasing the dose of inhaled steroid, consider a sequential trial of add-on therapy, i.e. leukotriene receptor antagonists, theophyllines, slow release  $\beta_2$  agonist tablets (this in adults only).

<b>2004</b>	Addition of <b>short-acting</b> anticholinergics is generally of no value. <sup>178,574</sup> Addition of nedocromil is of marginal benefit. <sup>179,675</sup>	> 12 years	5-12 years	< 5 years
<b>2005</b>		1 <sup>+</sup>		

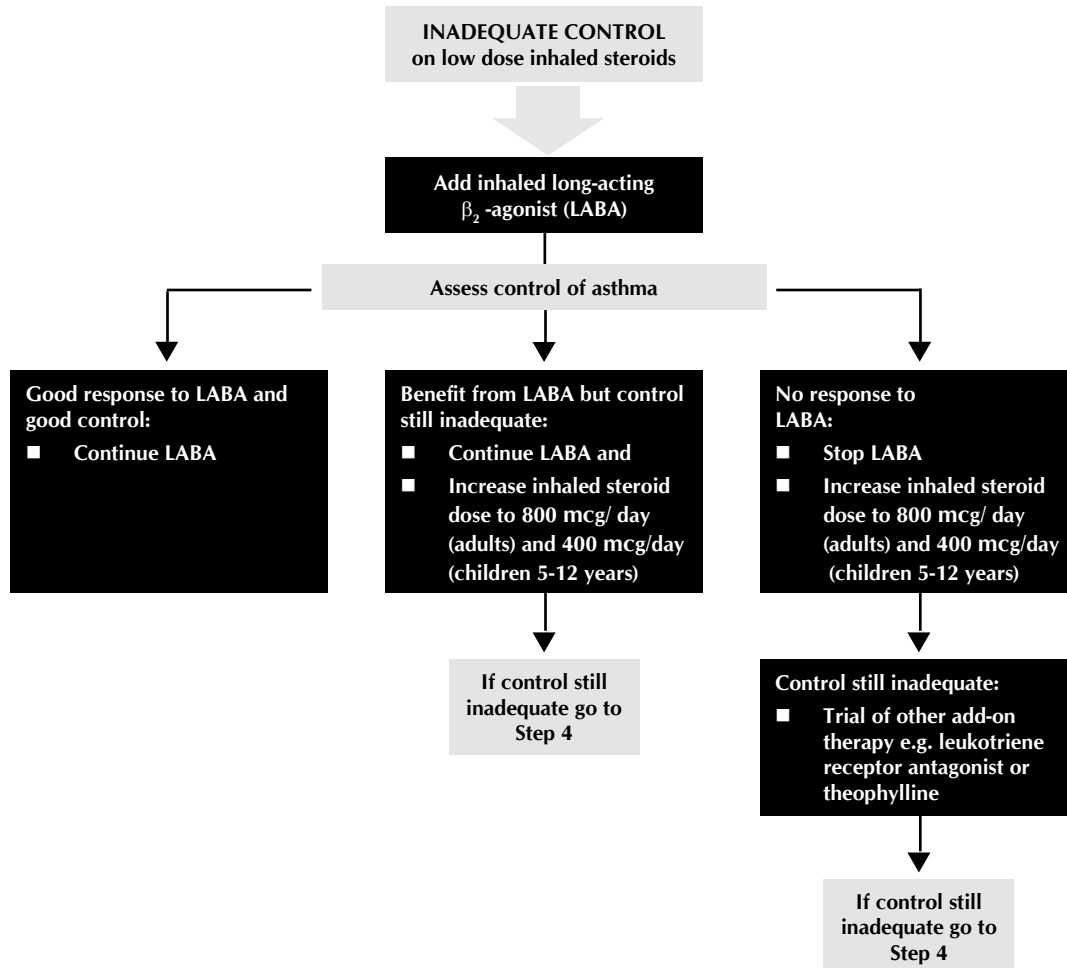
<b>2007</b>	In patients on inhaled steroids whose asthma is stable, no intervention has been consistently shown to decrease inhaled steroid requirement in a clinically significant manner compared to placebo.			
-------------	---	--	--	--

## 4.3.3 COMBINATION INHALERS

There is no difference in efficacy in giving inhaled steroid and long-acting  $\beta_2$  agonist in combination or in separate inhalers.<sup>182</sup>

>12 years	5-12 years	<5 years
1++	1++	

Figure 3: Summary of Step 3: Add-on therapy



#### 4.4 STEP 4: POOR CONTROL ON MODERATE DOSE OF INHALED STEROID + ADD-ON THERAPY: ADDITION OF FOURTH DRUG

In a small proportion of patients asthma is not adequately controlled on a combination of short-acting  $\beta_2$  agonist as required, inhaled steroid (800 mcg daily), and an additional drug, usually a long-acting  $\beta_2$  agonist. There are very few clinical trials in this specific patient group to guide management. The following recommendations are based on extrapolation from trials of add-on therapy to inhaled steroids and on previous guidelines.

D	D	<p><b>If control remains inadequate on 800 mcg daily (adults) and 400 mcg daily (children) of an inhaled steroid plus a long-acting <math>\beta_2</math> agonist, consider the following interventions:</b></p> <ul style="list-style-type: none"> <li>▪ increasing inhaled steroids to 2000 mcg/day (adults) or 800 mcg/day (children 5-12 years)</li> <li>▪ leukotriene receptor antagonists</li> <li>▪ theophyllines</li> <li>▪ slow release <math>\beta_2</math> agonist tablets, though caution needs to be used in patients on long-acting <math>\beta_2</math> agonists.</li> </ul>
---	---	--

There are no controlled trials indicating which of these is the best option.

- ✓ If a trial of an add-on treatment is ineffective, stop the drug (or in the case of increased dose of inhaled steroid, reduce to the original dose).
- ✓ Before proceeding to step 5, consider referring patients with inadequately controlled asthma, especially children, to specialist care.

#### 4.5 STEP 5: CONTINUOUS OR FREQUENT USE OF ORAL STEROIDS

##### 4.5.1 PREVENTION AND TREATMENT OF STEROID TABLET-INDUCED SIDE-EFFECTS

**2007** Patients on long-term steroid tablets (e.g. longer than three months) or requiring frequent courses of steroid tablets (e.g. three to four per year) will be at risk of systemic side-effects.<sup>676</sup>

- Blood pressure should be monitored.
- Diabetes mellitus and hyperlipidaemia may occur.
- **2007** Reduction in bone mineral density commonly occurs and should be monitored. When this occurs, those adults also receiving prednisolone for over three months should be prescribed a long-acting bisphosphonate (see new British Osteoporosis Society guidelines, [www.nos.org.uk](http://www.nos.org.uk)).<sup>185</sup>
- **2004** Growth should be monitored in children.
- **2007** Cataracts may be screened for in children through community optometric services.

4.5.2 STEROID TABLET-SPARING MEDICATION

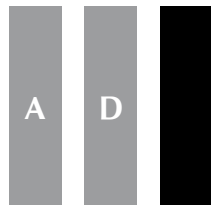
The aim of treatment is to control the asthma using the lowest possible dose or, if possible, to stop long-term steroid tablets completely.

Inhaled steroids are the most effective drug for decreasing requirement for long-term steroid tablets.<sup>162,163</sup>

> 12 years	5-12 years	< 5 years
1 <sup>++</sup>	4	

**2005**

There is limited evidence for the ability of long-acting  $\beta_2$  agonists, theophyllines, or leukotriene receptor antagonists to decrease requirement for steroid tablets, but they may improve symptoms and pulmonary function.<sup>192</sup>



- In adults, the recommended method of eliminating or reducing the dose of steroid tablets is inhaled steroids, at doses of up to 2000 mcg/day if required.
- In children aged 5-12, consider very carefully before going above a dose of 1000 mcg/day.

There is a role for a trial of treatment with long-acting  $\beta_2$  agonists, leukotriene receptor antagonists, and theophyllines for about six weeks. They should be stopped if no improvement in steroid dose, symptoms or lung function is detected.

Immunosuppressants (methotrexate, ciclosporin and oral gold) decrease long-term steroid tablet requirements, but all have significant side-effects. There is no evidence of persisting beneficial effect after stopping them; and there is marked variability in response.<sup>186</sup>

> 12 years	5-12 years	< 5 years
1 <sup>+</sup>	3	

**2007**



Immunosuppressants (methotrexate, ciclosporin and oral gold) may be given as a three month trial, once other drug treatments have proved unsuccessful. Their risks and benefits should be discussed with the patient and their treatment effects carefully monitored. Treatment should be in a centre with experience of using these medicines.

Colchicine and intravenous immunoglobulin have not been shown to have any beneficial effect in adults.<sup>186</sup>

> 12 years	5-12 years	< 5 years
1 <sup>+</sup>		
4		

**2007**

Continuous subcutaneous terbutaline infusion has been reported to be beneficial in severe asthma but efficacy and safety have not been assessed in RCTs.<sup>187,677</sup>

4.5.3 STEROID FORMULATIONS

Prednisolone is the most widely used steroid tablet for maintenance therapy in chronic asthma. There is no evidence that other formulations offer any advantage.

4.5.4 FREQUENCY OF DOSING OF STEROID TABLETS

Although popular in paediatric practice, there are no studies to show whether alternate day steroids produce fewer side-effects than daily steroids.

4.5.5 B-BLOCKERS

$\beta$ -blockers, including eye drops, are contraindicated in patients with asthma

Figure 4: Summary of stepwise management in adults

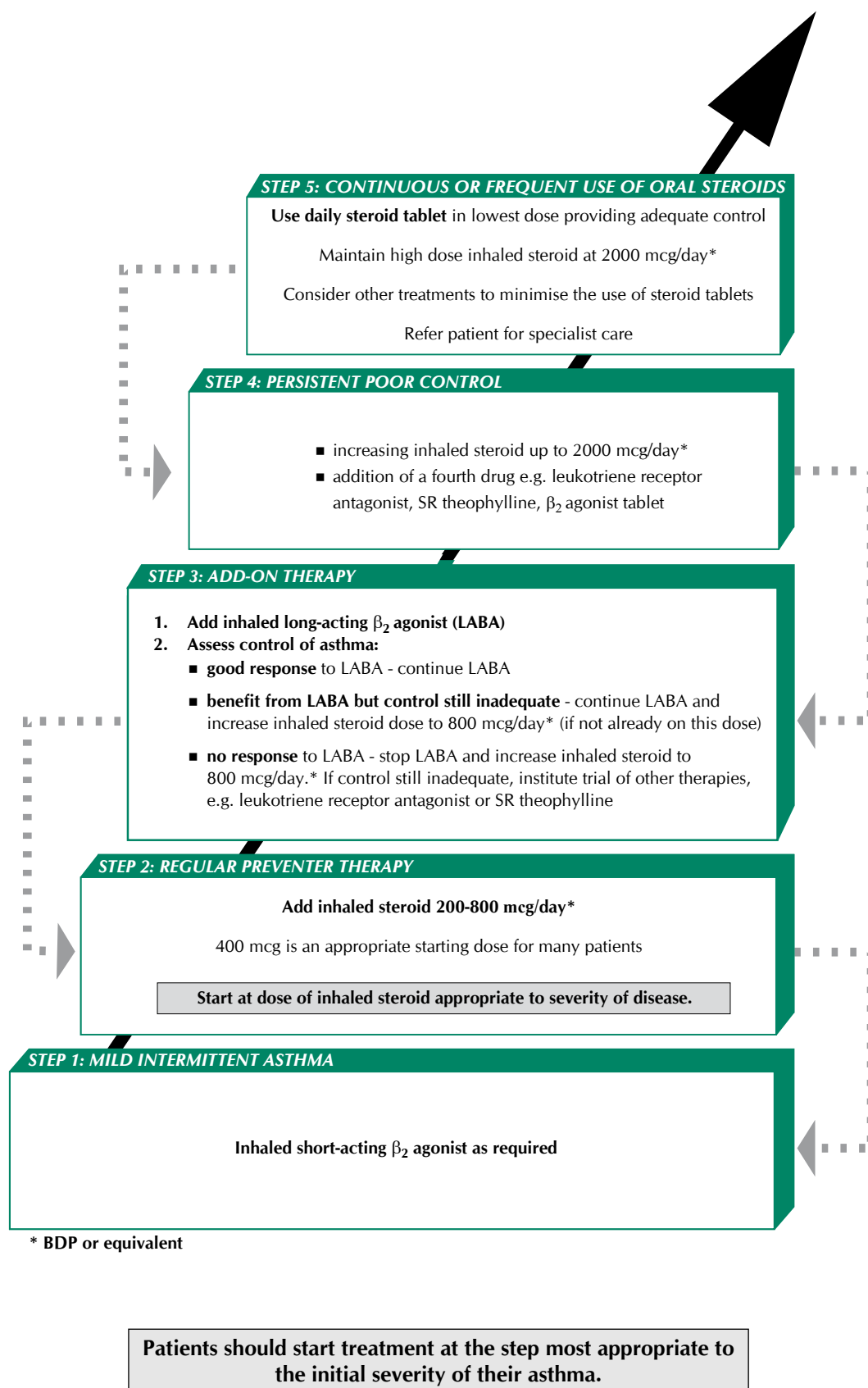
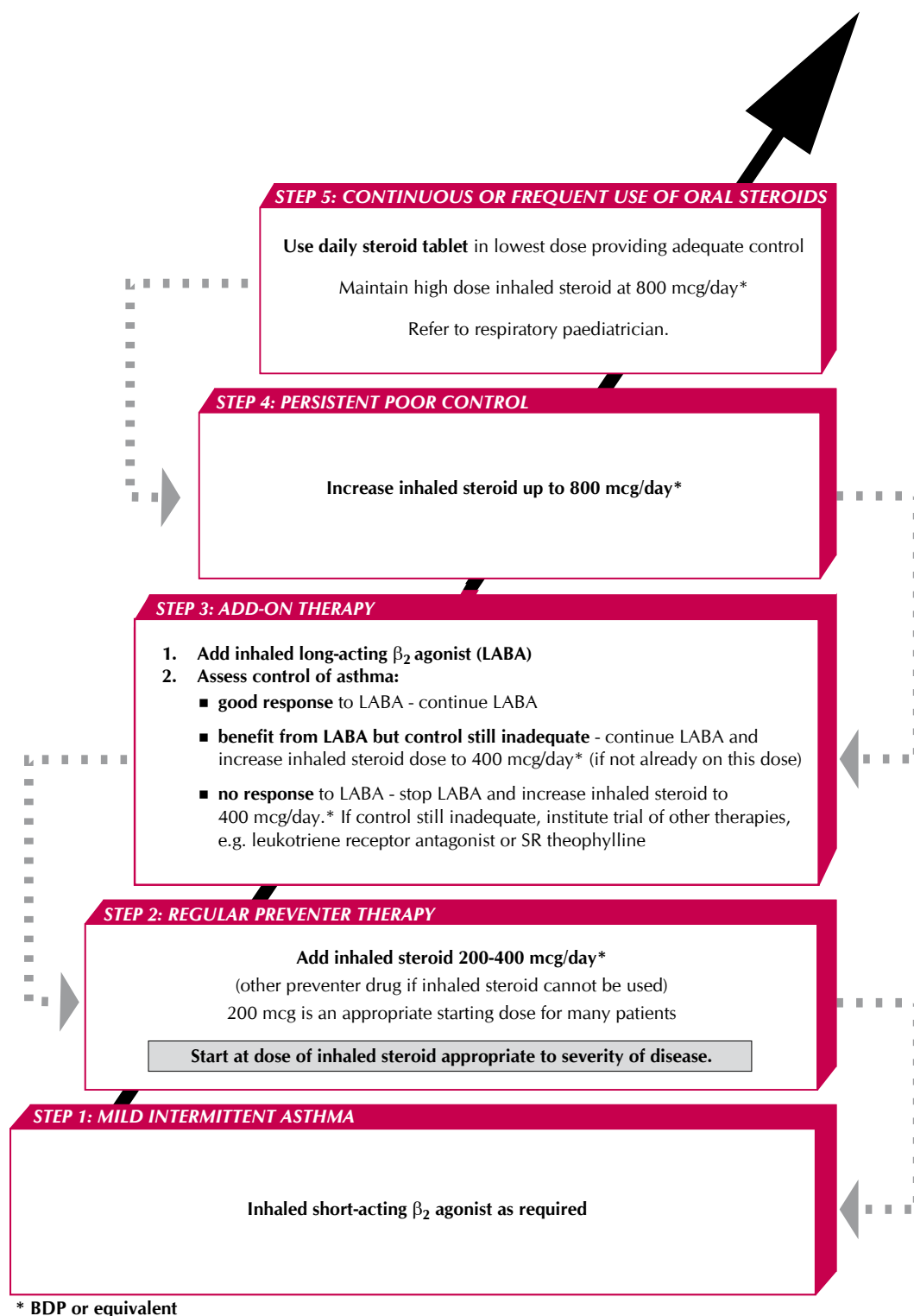
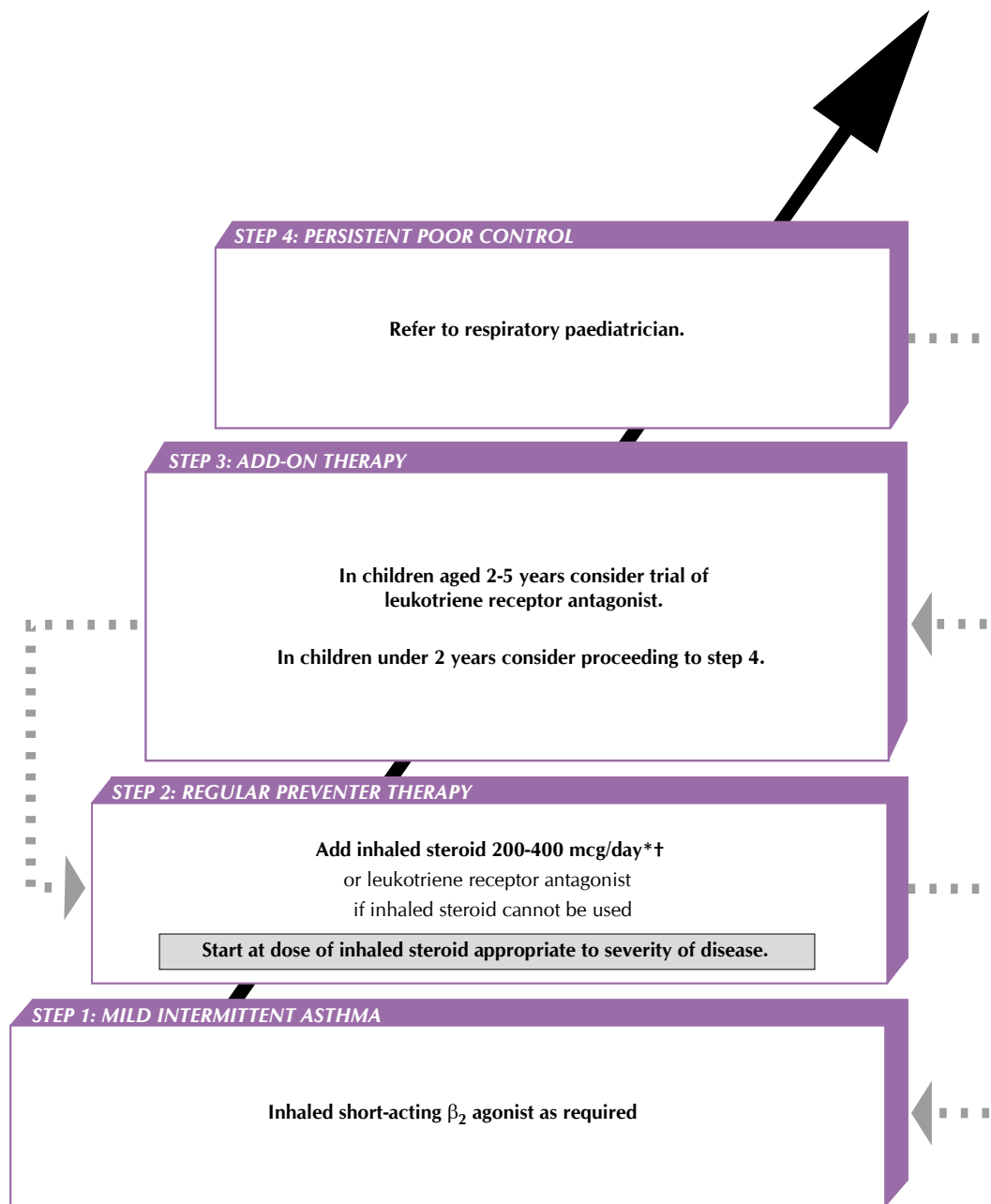


Figure 5: Summary of stepwise management in children aged 5 - 12 years



Patients should start treatment at the step most appropriate to the initial severity of their asthma.

Figure 6: Summary of stepwise management in children less than 5 years



\* BDP or equivalent

† Higher nominal doses may be required if drug delivery is difficult

Patients should start treatment at the step most appropriate to the initial severity of their asthma.

## 4.6 STEPPING DOWN

2004

Stepping down therapy once asthma is controlled is recommended, but often not implemented leaving some patients over-treated. There are few studies that have investigated the most appropriate way to step down treatment. A study in adults on at least 900mcg per day of inhaled steroids has shown that for patients who are stable it is reasonable to attempt to halve the dose of inhaled steroids every three months.<sup>530</sup>

✓

Regular review of patients as treatment is stepped down is important. When deciding which drug to step down first and at what rate, the severity of asthma, the side-effects of the treatment, the beneficial effect achieved, and the patient's preference should all be taken into account.

✓

Patients should be maintained at the lowest possible dose of inhaled steroid. Reduction in inhaled steroid dose should be slow as patients deteriorate at different rates. Reductions should be considered every three months, decreasing the dose by approximately 25-50% each time.

## 4.7 SPECIFIC MANAGEMENT PROBLEMS

### 4.7.1 ONSET OF EXACERBATION OF ASTHMA

2004

Although recommended for both adults and children in previous guidelines and as part of asthma action plans, doubling the dose at the time of an exacerbation is of unproven value.<sup>188</sup>

2005

In adult patients on a low dose (200 mcg) of inhaled steroids, a five-fold increase in dose at the time of exacerbation leads to a decrease in the severity of exacerbations.<sup>188,575</sup> This study should not be extrapolated to patients already taking higher doses of inhaled steroids and further evidence in this area is required.

2007

In adults doubling the dose of inhaled steroids at the time of exacerbation has not been shown to be effective. Studies in which the dose of a combination inhaler budesonide/formoterol is adjusted according to symptoms have shown good levels of asthma control.<sup>678</sup> It is not clear if this is superior to the use of more conventional stable dose of inhaled steroids and long acting  $\beta_2$  agonists. This study should not be extrapolated to patients already taking high doses of inhaled steroids.

### 4.7.2 EXERCISE-INDUCED ASTHMA

✓

For most patients, exercise-induced asthma is an expression of poorly controlled asthma and regular treatment including inhaled steroids should be reviewed.

The following medicines give protection against exercise-induced asthma: inhaled steroids<sup>162,163,189</sup>

- short-acting  $\beta_2$  agonists<sup>157</sup>
- long-acting  $\beta_2$  agonists<sup>190</sup>
- theophyllines<sup>191,192</sup>
- leukotriene receptor antagonists<sup>193</sup>
- chromones<sup>194</sup>
- $\beta_2$  agonist tablets.<sup>195</sup>

The following medicines do not give protection against exercise-induced asthma at normal doses:

- anticholinergics<sup>196</sup>
- ketotifen<sup>197</sup>
- antihistamine.<sup>198</sup>

	> 12 years	5-12 years	< 5 years
	1++	1++	
	1++	1++	
	1++	1++	
	1-	2+	
	1++	2+	
	1++	2+	
	1++	1+	
	1+	1+	
	1+	1+	
	1++	1++	

Long-acting $\beta_2$ agonists and leukotriene antagonists provide more prolonged protection than short-acting $\beta_2$ agonists, but a degree of tolerance develops with LABA particularly with respect to duration of action. No tolerance has been demonstrated with leukotriene receptor antagonists. <sup>190,193</sup>	>12 years 1 <sup>++</sup>	5-12 years	<5 years
---	------------------------------	------------	----------

**If exercise is a specific problem in patients taking inhaled steroids who are otherwise well controlled, consider the following therapies:**

A	C	■	▪ leukotriene receptor antagonists
A	A	■	▪ long-acting $\beta_2$ agonists
C	C	■	▪ chromones
A	A	■	▪ oral $\beta_2$ agonists
C	C	■	▪ theophyllines.
A	A	✓	<b>Immediately prior to exercise, inhaled short-acting <math>\beta_2</math> agonists are the drug of choice.</b>

4.7.3	RHINITIS	>12 years 1 <sup>+</sup>	5-12 years	<5 years
	Patients with asthma often have rhinitis. The most effective therapy is intranasal steroids. <sup>199</sup> Treatment of allergic rhinitis has not been shown to improve asthma control.			

4.7.4	ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS	>12 years 1 <sup>+</sup>	5-12 years	<5 years
<b>2005</b>	In adult patients with allergic bronchopulmonary aspergillosis (ABPA), itraconazole may decrease steroid tablet dose and improve asthma control. <sup>518,576</sup>			

C	■	■	<b>In adult patients with ABPA, a four month trial of itraconazole should be considered.</b>
✓	Careful monitoring for side-effects, particularly hepatic is recommended.		

4.7.5 ASPIRIN-INTOLERANT ASTHMA

There are theoretical reasons to suggest that leukotriene receptor antagonists might be of particular value in the treatment of aspirin intolerant asthma. However, there is little evidence to justify managing patients with aspirin intolerant asthma in a different manner to patients tolerant of aspirin, apart from the rigorous avoidance of non-steroidal anti-inflammatory medications.<sup>200</sup>

## 4.8 ANTI IGE MONOCLONAL ANTIBODY

2007

Omalizumab is a humanised monoclonal antibody which binds to circulating IgE markedly reducing levels of free serum IgE.<sup>679,680</sup> In adults and children over 12, it is licensed in the UK with the following indication; patients on high dose inhaled steroids and long acting  $\beta_2$  agonists who have impaired lung function are symptomatic with frequent exacerbations, and have allergy as an important cause of their asthma. Omalizumab is given as a subcutaneous injection every 2 to 4 weeks depending on dose. The total IgE must be less than 700iu/litre for it to be effective.

In the single study in the licensed group, there was a 19% reduction in exacerbations of asthma requiring oral steroids which was non-significant. When corrected for imbalance in the exacerbation history at baseline, there was a 26% reduction in severe exacerbations (0.91 on placebo vs 0.68 on omalizumab over a 28 week period)  $p=0.042$ . This was associated with a 2.8% increase in FEV1, a non-significant 0.5 puffs/day decrease in  $\beta_2$  agonist use and 13% more patients having a significant improvement in health related quality of life. At IgE levels below 76iu/l the beneficial effect is reduced.

Apart from local reactions there appear to be no major safety issues. There are no active comparative studies and it is therefore not possible to place omalizumab in the stepwise treatment of asthma.

Anaphylaxis, presenting as bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue has been reported to occur after administration of omalizumab. Anaphylaxis has occurred as early as after the first dose, but also has occurred beyond one year after beginning regular treatment.

Due to the risk of anaphylaxis, omalizumab should only be administered to patients in a healthcare setting under direct medical supervision. For further information see [www.fda.gov/cder/drug/InfoSheets/HCP/omalizumabHCP.pdf](http://www.fda.gov/cder/drug/InfoSheets/HCP/omalizumabHCP.pdf)