

NEWSLETTER

Supporting the North Derbyshire Health Community

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PACEF update

The current Traffic Lights list can be accessed via your PCT website (www.chesterfieldpct.nhs.uk, www.highpeakanddalespct.nhs.uk, or www.northeasternderbyshirepct.nhs.uk) or the PACEF intranet site www.nodyis.nhs.uk/guidelines/pacef%20web.htm.

RED drugs are those where prescribing responsibility would normally lie with a hospital consultant or a specialist. AMBER drugs are those that although usually initiated within a hospital setting, could appropriately become the responsibility of the GP. This would normally be under a shared care agreement. GREEN drugs are regarded as routine for primary care prescribing. BROWN drugs are those that PACEF does not recommend for use (or only in restricted circumstances) due to lack of data on safety, effectiveness, or cost-effectiveness.

<u>Drug</u>	<u>Date considered</u>	<u>Decision</u>
Desloratidine	July 2006	BROWN
Levocetirizine	July 2006	BROWN
Pegaptanib injection	July 2006	RED
Rotigotine patch	July 2006	BROWN
Zaleplon	July 2006	BROWN
Zolpidem	July 2006	BROWN
Zopiclone	July 2006	BROWN
Atimos Modulite (formoterol cfc-free MDI)	June 2006	GREEN
Letrozole	June 2006	AMBER
Acamprosate	April 2006	AMBER (moved from RED)
Ivabradine	April 2006	BROWN
Nebivolol	April 2006	BROWN
Revatio (sildenafil 20mg tablet for PAH)	April 2006	RED
Inhaled insulin (Exubera)	April 2006	RED

Inhaled insulin (Exubera)

In April NICE issued its preliminary recommendations on the use of inhaled insulin for the treatment of diabetes as follows:

'Inhaled insulin is not recommended for the treatment of type 1 or type 2 diabetes mellitus, except in the context of clinical studies designed to evaluate the clinical and cost effectiveness of inhaled insulin compared with injected insulin in people with diabetes whose blood sugar levels are uncontrolled with their current diabetes regimen. These studies should include relevant outcome measures to evaluate quality of life'.

Given the evidence on clinical effectiveness and cost effectiveness, the Committee concluded that inhaled insulin should not be recommended for the diabetic (type 1 or type 2) population as a whole. Furthermore, inhaled insulin should not be recommended for patients whose blood glucose levels remained uncontrolled because of a very strong aversion to insulin injections. The Committee reached this conclusion because there is (1) currently insufficient evidence of clinical effectiveness in this patient group and (2) uncertainty about how to identify this patient group in routine clinical practice with the accuracy necessary to ensure cost effectiveness.

This preliminary guidance received much press interest with condemnation from Pfizer and Diabetes UK.

Last month NICE issued the following revised preliminary recommendations on inhaled insulin:

- Inhaled insulin is not recommended for the routine treatment of people with type 1 or type 2 diabetes mellitus.
- Inhaled insulin is recommended as a treatment option in patients with type 1 or type 2 diabetes mellitus who have a HbA1c level 9% or higher, despite other therapeutic interventions (including diet and oral hypoglycaemic agents) and adequate educational support, AND who are unable to start or intensify insulin therapy because of either a proven injection phobia diagnosed by a psychiatrist/psychologist, OR severe persistent problems with injection sites (e.g. lipohypertrophy)
- Treatment in suitable patients should only be continued beyond 6 months if a decrease in HbA1c level >1% is achieved and the level is maintained at <10%.
- Initiation of inhaled insulin treatment and monitoring of response should be carried out only by a specialist centre.

This is still a draft document, out for comment, and PACEF has recommended that until the final NICE guidance is published, inhaled insulin should not be prescribed across North Derbyshire.

Atimos Modulite (formoterol cfc-free MDI)

Formoterol is now available as a CFC-free pMDI marketed under the brand name Atimos Modulite. Formoterol and salmeterol are equally effective as long-acting beta-agonists but formoterol has a quicker onset of action. The recommended first-line inhalation device is a pMDI.

Atimos has a considerable cost advantage over alternative formulations of LABAs.

Cost comparison of long-acting β_2 agonists

Product	Long-Acting B_2 agonist	Dose	28 day cost
Atimos Modulite 12mcg	Formoterol	12mcg b.d.	£17.52
Oxis Turbohaler 6mcg	Formoterol	12mcg b.d.	£46.30
Oxis Turbohaler 12mcg	Formoterol	12mcg b.d.	£23.15
Foradil 12mcg Inhaled capsules	Formoterol	12mcg b.d.	£24.80
Serevent pMDI 25mcg	Salmeterol	50mcg b.d.	£27.31
Serevent Accuhaler 50mcg	Salmeterol	50mcg b.d.	£27.31
Serevent Diskhaler 50mcg	Salmeterol	50mcg b.d.	£33.40
Serevent Diskhaler 50mcg refill	Salmeterol	50mcg b.d.	£32.80

Cost comparison of combination inhalers

Seretide Evohaler 25/125	Salmeterol with fluticasone	2 puffs b.d.	£34.21
Seretide Acculater 50/250	Salmeterol with fluticasone	1 puff b.d.	£34.21
Symbicort 100/6 Turbohaler	Formoterol with budesonide	2 puffs b.d.	£30.80
Symbicort 200/6 Turbohaler	Formoterol with budesonide	2 puffs b.d.	£35.47

Prescribing Qvar 100 (beclometasone CFC-free) 2 puffs b.d. (£9.64) with Atimos (£17.52) would cost £27.16

Atimos Modulite is currently licensed for persistent, moderate to severe asthma in those aged 12 years and above. It is licensed for COPD in some European countries and the UK COPD licence is expected in late 2006.

PACEF has discussed Atimos and classified it as GREEN in the traffic light list and recommends inclusion in formularies as the first-choice LABA. In addition, consideration should be given to switching from other LABA formulations to Atimos in order to release scarce resources. It can be prescribed generically as formoterol CFC-free MDI 12 micrograms.

Switching statins

An editorial in the BMJ provides strong support for the North Derbyshire Statin Policy. The authors even go a stage further and recommended that prescriptions for atorvastatin 10mg **and** 20mg are switched to simvastatin 40mg¹. They say that this would have no effect on health but would save £1.1 billion over 5 years.

They quote a meta-analysis of clinical trials that shows no significant differences in mortality, death from CHD, or stroke using simvastatin 40mg or atorvastatin 10mg. No trial directly supports the effectiveness of atorvastatin 20mg. In controlled dosing studies, simvastatin 40mg and atorvastatin 10mg and 20mg are equally effective at lowering lipid levels¹.

Have you switched yet? It would release much needed resources.

1. BMJ 2006; 332:1344-5

Ambulatory BP monitoring

The bulk of our knowledge about the risks of hypertension and the benefits of treating it is based on the traditional method of taking a small number of BP readings with the auscultatory technique in a medical setting. Ambulatory monitoring was not available when the Framingham study started, and hence it is not appropriate to use ambulatory readings directly into CV risk charts based on Framingham.

It is claimed that ambulatory BP predicts CV events better than clinic blood pressure does, but it is uncertain which component of the 24-hour BP profile gives the best prediction of risk¹. NICE recommends that "routine use of automated ambulatory blood pressure monitoring or home monitoring devices in primary care is not currently recommended because their value has not been adequately established; appropriate use in primary care remains an issue for further research"².

BHS IV³ suggests the following potential indications for the use of ambulatory BP monitoring:

- Unusual BP variability
- Possible 'white-coat' hypertension (HTN)
- Informing equivocal treatment decisions
- Evaluation of nocturnal HTN
- Evaluation of drug-resistant HTN
- Determining efficacy of drugs over 24 hours
- Diagnosis/treatment of HTN in pregnancy
- Evaluation of symptomatic hypotension

The daytime level of ambulatory BP that is usually considered the upper limit of normal is 135/85mmHg¹. This corresponds approximately to a clinic BP of 140/90¹.

White-coat hypertension (WCH)

WCH is the only indication for ambulatory BP monitoring approved by Medicaid and Medicare Services in the U.S. Suspected WCH is defined as clinic BP of 140/90 or higher on at least 3 occasions, with at least 2 sets of measurements of less than 140/90 in non-clinic settings, plus the absence of target-organ damage¹. Studies have shown that drug treatment of WCH reduces the clinic BP but has negligible effect on ambulatory BP, which is by definition normal. In addition, the only study to investigate the effects of treating WCH on morbid events found no significant benefit¹. Sustained hypertension may develop in some patients with WCH and

long-term follow-up with repeated ambulatory BP monitoring or home monitoring has been recommended¹. WCH does not warrant antihypertensive drug treatment¹ and as Little points out “the overzealous initiation and maintenance of treatment for WCH represents an enormous opportunity cost for health professionals and for patients, in addition to the associated iatrogenesis – particularly unnecessary anxiety and side effects”⁴.

Little found that BP readings made by doctors were much higher than ambulatory systolic pressure by a mean of 18.9mmHg (confirming the “white coat” effect) and recommended that it is time to stop using high BP readings documented by GPs to make treatment decisions⁴. If ambulatory or home measurements are not available, repeated measurements by the nurse or patient should result in considerably less unnecessary monitoring, initiation, or changing of treatment, he adds.

NICE recommends that patients with persistent high clinic blood pressure of 160/100 or more need drug treatment to be started². Little suggests that this level corresponds to an ambulatory BP of greater than 145/95 mmHg⁴. BHS IV advises that when using ambulatory BP readings, mean daytime pressures are preferred and this value would be expected to be approximately 10/5 mmHg lower than the office BP equivalent for both thresholds and targets.

What should we do?

Clinic BP measurements should be carried out as advised by NICE² by a trained health professional (preferably a nurse?⁴) using a validated and properly maintained device, and where possible, in a standardised environment. Take the mean of 2 readings on at least 3 separate occasions.

Use ambulatory BP monitoring if white coat hypertension is suspected. If the mean of daytime ambulatory BP is 135/85 or less, no treatment is required but annual follow-up may be appropriate. If ambulatory BP is greater than 145/95, initiate treatment. For mean daytime readings in-between these 2 values, add 10/5 to the value and use the standard risk assessment tool to calculate overall risk.

1. Pickering TG et al. N Engl J Med 2006; 354:2368-74
2. NICE Clinical Guideline 34. June 2006
3. BHS IV. BMJ 2004; 328:634-40
4. Little P et al. BMJ 2002; 325:254-60

Beta-blockers for hypertension

Further to the meta-analysis reported in the November 2005 edition of this newsletter in which the authors concluded that beta-blockers should not remain one of the first choice options for the treatment of hypertension, another meta-analysis re-examines the data¹. The authors of this new meta-analysis argue that because the pathophysiology of hypertension differs in older and younger patients, it makes sense to clarify the effectiveness of beta-blockers in different age groups.

They analysed 21 RCTs (with 145,811 participants) evaluating beta-blockers as first-line therapy for hypertension in preventing major cardiovascular outcomes. The primary outcome of the analysis was a composite of stroke, MI and death. Trials enrolling older (mean age \geq 60 years) were separated from those enrolling younger (mean age < 60 years) patients.

They found that their results confirmed the findings of the previous meta-analysis that beta-blockers are associated with an increased risk of stroke compared with other antihypertensive agents, but the results show that this excess risk is largely driven by data from trials enrolling older patients. Younger patients randomly assigned to beta-blockers exhibited similar rates of CV deaths, MI or stroke to those assigned other antihypertensive agents.

The authors conclude that although beta-blockers should not be considered first-line therapy for older hypertensive patients without another indication (such as heart failure, post MI or symptomatic coronary disease), in younger patients with contraindications or intolerance to thiazide diuretics then the analysis supports the use of beta-blockers as a first-line agent for lowering blood pressure.

1. CMAJ 2006; 174:1737-42

ACE inhibitors and congenital malformations

ACE inhibitors and angiotensin–II antagonists are contraindicated in pregnancy. When used in the second half of pregnancy, ACEIs can cause oligohydramnios fetal growth retardation, pulmonary hypoplasia, joint contractures, hypocalvaria and neonatal renal failure, hypotension and death¹.

A recent study assessed the association between exposure to ACEIs during the first trimester of pregnancy and the risk of congenital malformations². They found that infants with only first trimester exposure to ACEIs had an increased risk of major congenital malformations (risk ratio 2.71; CI 1.72 to 4.27) as compared with infants who had no exposure to antihypertensive medications. The contrast, fetal exposure to other antihypertensive medications during only the first trimester did not confer an increased risk (risk ratio 0.66; CI 0.25 to 1.75). Infants exposed to ACEIs were at particularly increased risk for malformations of the cardiovascular system (RR 3.72) and the CNS (RR 4.39).

The authors concluded that exposure to ACEIs during the first trimester cannot be considered safe and should be avoided. The accompanying editorial recommends that a woman who learns that she is pregnant while taking an ACEI should be immediately switched to another antihypertensive agent². It may be safer to avoid the use of ACEIs in women of childbearing age if at all possible.

1. NEJM 2006; 354:2498-500
2. NEJM 2006; 354:2443-51

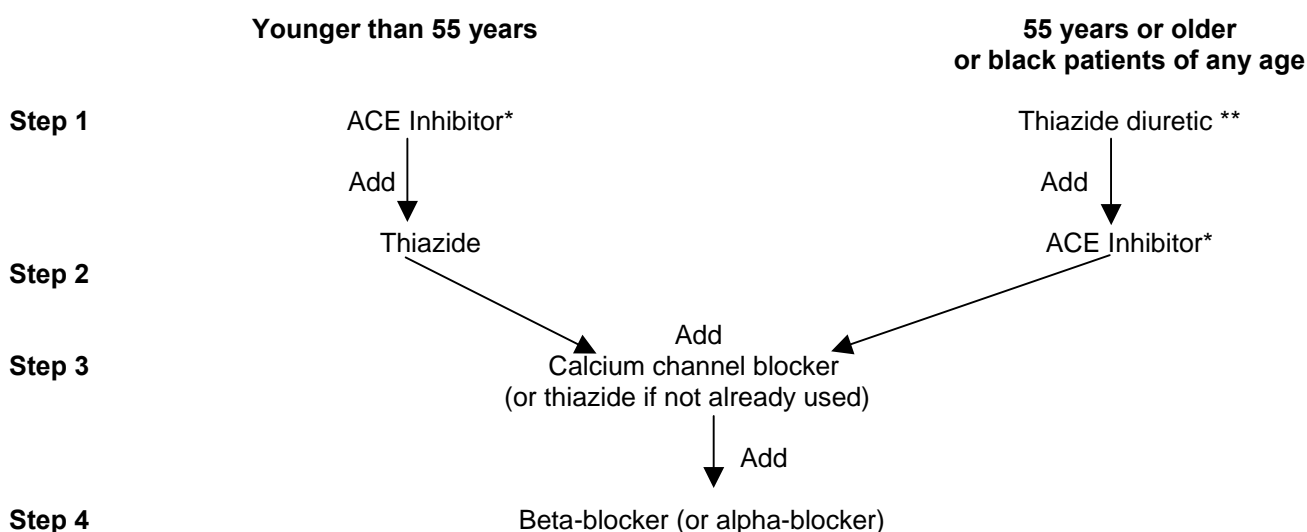
Updated hypertension guideline

The updated NICE guideline on the management of hypertension in adults in primary care has now been published.

Beta-blockers are no longer preferred as a *routine* initial therapy but that does not mean that they are never appropriate. If a patient's blood pressure is well controlled (140/90 or less) by a regimen that includes a beta-blocker, consider long-term management at their routine review. There is no absolute need to replace the beta-blocker in this case. If a patient's blood pressure is not well controlled by a regimen that includes a beta-blocker (above 140/90), change their treatment using the following flow chart. When withdrawing a beta-blocker, step down the dose gradually. Do not withdraw beta-blocker if a patient has a compelling indication for being treated with one (angina, MI, heart failure).

The following flow chart for choosing initial and additional anti-hypertensives has been approved by PACEF. ***Thiazides remain first-line in most people needing treatment for raised blood pressure.***

Choosing drugs to lower blood pressure and reduce cardiovascular risk



* use angiotensin-II antagonist if ACEI intolerant

** use calcium channel blocker if thiazide contraindicated or not tolerated

Beta-blockers

- Are no longer preferred as a routine initial therapy for hypertension
- May be appropriate for those who have another indication for beta-blocker therapy – angina, previous MI, heart failure
- Should be considered for some younger people, particularly:
 - women of childbearing potential
 - patients with evidence of increased sympathetic drive
 - patients with intolerance of or contraindications to ACE inhibitors and angiotensin-II antagonists

The aim is to reduce blood pressure to 140/90 or less, adding drugs as needed, *until further treatment is inappropriate or declined.*

Updated prescribing advice for venlafaxine

The MHRA has updated its advice on the prescribing of venlafaxine. It is less restrictive than before.

The NICE advice that venlafaxine should be reserved as a second-line treatment (after SSRIs) still stands. The following changes have been authorised in line with the review of the evidence:

- **Specialist supervision** (including shared care arrangements) is now only required for initiation of venlafaxine treatment in those severely depressed or hospitalised patients who require doses of 300mg daily, or above.
- **Contra-indications and warnings:** Venlafaxine is contraindicated in patients with an identified high risk of a serious cardiac ventricular arrhythmia. Venlafaxine remains contra-indicated in patients with uncontrolled hypertension.
- The contra-indications for patients with an electrolyte imbalance and the requirement for a baseline ECG have been removed from product information.
- Venlafaxine should be used with caution in patients with established cardiac disease that may increase the risk of ventricular arrhythmias (e.g. recent myocardial infarction).
- Regular measurement of blood pressure is recommended for patients receiving venlafaxine. For patients who experience a sustained increase in blood pressure while receiving venlafaxine, either dose reduction or discontinuation should be considered.
- **Interactions:** Potent CYP3A4 inhibitors (e.g. ketoconazole, erythromycin) or drug combinations that inhibit both CYP3A4 and CYP2D6 should only be co-administered with venlafaxine when strictly indicated, because of the possibility of clinically important interactions in patients with a 'poor metaboliser' phenotype. Specialist supervision is recommended for use of concomitant SSRIs.

Minimising the risk of overdose

Smaller pack sizes will be available within the coming months. Patients with increased risk factors for suicide should be carefully evaluated for the presence of worsening of suicide related behaviour; a maximum of two weeks supply should be considered for high-risk patients at initiation of treatment, during any dosage adjustment and until improvement occurs.

Action

- Prescribing for new patients should be in line with the updated prescribing advice. An updated, user-tested, patient information leaflet will be available from the manufacturer in the coming months.
- Patients already established on venlafaxine should have a routine treatment review to ensure that their treatment is in line with the latest recommendations (for example cardiac risks, blood pressure and concomitant medicines).

This was discussed at PACEF and the decision taken to keep venlafaxine as a third-line option and to keep it as an AMBER drug.

Wasted medicines and avoidable adverse events

Medication errors are reasonably common. A UK survey of adverse drug reactions (ADRs) causing hospital admission found that they accounted for 6.5% of all admissions¹ (see PACE Newsletter September 2004). The majority of these were assessed as avoidable. Another UK study looked at the root causes of preventable

ADRs and this supports the view that the most important and rectifiable cause of problems is faulty prescribing². The study found that the commonest underlying causes for ADR-related general medical admissions were:

- Prescribing error (35% of total)
- Failed therapeutic monitoring (26%)
- Incorrect medication adherence (30%)

A recent paper highlights that avoidable adverse events and wasted medicines are a multimillion-pound problem³. The author quotes that each year patients return medicines worth at least £100 million unused to pharmacies. This is probably the tip of an iceberg as many people dispose of their medication rather than return it to the pharmacy. This non-compliance not only wastes scarce resources but also increases the likelihood that patients will develop adverse outcomes. Improving compliance is critical to both improving outcomes and reducing wastage. The author estimates that the total cost of potentially avoidable ADRs in the community and secondary care is approximately £1 billion a year.

A publication from the Medical Protection Society entitled “Bad medicine” looks at how prescribing practice can be improved to enhance patient safety. They offer the ‘ABC of safe prescribing’, 6 tips for prescribing safety, and tables of drugs that frequently cause avoidable ADRs and important drug interactions. If you would like a copy just ask and I can provide one.

1. BMJ 2004; 329:15-19
2. Qual Saf Health Care 2003; 12:280-85
3. J Med Economics 2006; 9:27-44

Which drug regimens can be used to suppress menstruation for a woman going on holiday?

This has been something of a hot-topic recently with a number of enquiries regarding the choice of agent to postpone menstruation. Suppression of menstruation may be desired by women going on holiday and also for women travelling to places of pilgrimage or participating in sporting events.

For women taking a combined oral contraceptive, skipping a period can be achieved by taking the pill continuously, without the usual seven-day break in between packets. Contraceptive efficacy is not reduced and some products include information on how to skip a period in their Summary of Product Characteristics. It is not advisable to take biphasic or triphasic pills without a break because the dose in the first seven pills may be too low to prevent possible breakthrough bleeding.

Norethisterone is licensed for the postponement of menstruation in special circumstances (the SPC lists operations, travel and sports as examples). The dose is 5mg three times daily, starting three days before the expected onset of menstruation. A normal period should occur two to three days after the patient has stopped taking the tablets. Norethisterone is suitable for women unable to take combined oral contraceptives because of their oestrogen content.

The answer to this query was provided by the North West Medicines Information Service.

Updated shared care guideline for DMARDs in RA

This document has been ratified by PACEF. There are some changes to highlight.

For the gold compounds auranofin and myocrisin, >1+ proteinuria on >1 occasion, is a reason to stop the drug. This also applies to D-penicillamine. In addition, >1+ haematuria on >1 occasion, is a reason to stop D-penicillamine.

The updated regular monitoring requirements for methotrexate (oral and parenteral) are:

- FBC, differential WBC and platelets (2-3 days after medication) at 2, 4, and 6 weeks, then monthly thereafter
- LFT at 2, 4, 6, and 10 weeks, then 3 monthly thereafter
- U & E, creatinine every 6 months
- Monitor FBC 2 weeks after any dose increase
- Ask about respiratory symptoms at monitoring visit.

Effect of long-acting beta-agonists on severe asthma exacerbations and asthma-related deaths

After the FDA received post marketing reports of several asthma related deaths associated with salmeterol, the Salmeterol Multicenter Asthma Research Trial (SMART) was performed. The results of this study were highlighted in two recent editorials^{1,2}. Patients were randomly assigned to receive either salmeterol or placebo in addition to their usual therapy.

More than 26,000 participants were followed for 28 weeks and the study found a 4-fold increased risk for asthma-related deaths in the salmeterol group ($p=0.02$). One death was attributable to salmeterol for every 700 patient-years of treatment¹. One of the editorials suggested that "until the manufacturers of these drugs undertake the appropriate studies needed to clear the air, the safety of long-acting beta-agonists will remain uncertain"¹. The other raised the issue that "there is no evidence to support the use of long-acting beta2-agonists as standard add-on treatment in paediatric asthma when asthma is not adequately controlled on inhaled corticosteroids"².

In July 2005, an advisory panel to the FDA met to examine whether long-acting beta-agonists (LABAs) should be taken off the market. The panel concluded that strong warnings of increased risk should be placed on the labelling of all LABAs, with recommendations that they be used only after other drugs have failed.

The effect of LABAs on asthma-related deaths could perhaps be more precisely estimated by pooling the results of many trials. A recent meta-analysis attempts to do this and to assess the effect of LABAs on severe asthma exacerbations requiring hospitalisation, life-threatening asthma attacks and asthma-related deaths³.

Results

- The odds ratio (OR) for hospitalisation for asthma exacerbations was 2.6 (CI 1.6 to 4.3) for LABAs compared to placebo. The risk difference for hospitalisation attributed to LABAs was 0.7% over 6 months (NNH = 143). Results for children and adults were not significantly different, nor were those comparing salmeterol and formoterol.
- Trials in which more than 75% of participants were receiving concomitant inhaled steroids were separately evaluated. The risk for hospitalisation was still increased 2-fold (OR 2.1 [CI 1.3 to 3.4]).
- The OR for life-threatening asthma attacks attributed to LABAs was 1.8 (1.1 to 2.9), with a risk difference of 0.12% over 6 months (NNH = 833).
- The pooled risk difference for asthma-related deaths was 0.07% over 6 months (NNH = 1428).

Discussion

- This analysis showed that LABAs increased the risk for hospitalisation for an asthma exacerbation, life-threatening asthma attacks, and asthma-related deaths compared with placebo.
- This risk appears to still exist even with the use of concomitant inhaled steroids, at least for hospitalisations, and patients may not be adequately protected by their inhaled corticosteroid (ICS).
- The authors of this analysis surmise that salmeterol may be responsible for approximately 4000 of the 5000 asthma-related deaths that occur in the United States each year.
- LABAs may worsen control by means of a negative feedback mechanism of the beta-adrenergic system that is an adaptive response to stimulation of receptors involving desensitisation and downregulation. These effects may worsen asthma control without giving any warning of increased symptoms.

Recommendations (endorsed by PACEF)

- It is important to follow current guidelines and emphasise the use of ICS as the first-line treatment for patients with mild to moderate asthma symptoms. LABAs should not be used as initial therapy for any asthmatic patient.
- Make sure individuals are receiving an adequate dose of ICS. Escalate the dose of ICS to the levels recommended in the British Asthma Guideline (800mcg/day beclometasone equivalent in adults and 400mcg/day in children aged 12 and under) before considering a LABA. Do not jump to step 3 too early (this might be encouraged by the use of combination inhalers). If satisfactory control is not obtained at these doses then a LABA should be added.
- Do not move to step 3 without assessing inhaler technique and compliance. Encourage the use of spacer devices. Data show that in patients with more severe disease who still require two or more daily administrations of salbutamol in addition to adequate doses of ICS, symptoms in one third to one half may be explained by nonadherence to therapy or the coexistence of other conditions that are not responsive to beta-agonists¹.
- If at step 3, review regularly as recommended by the British Asthma Guideline, and consider stepping down back to step 2.
- It is important to carefully monitor patients on LABAs to identify those who do not respond or whose condition deteriorates in response to LABA therapy. Health professionals should be prepared to provide an alternative medication for patients in whom LABA therapy fails⁴.
- Remember that the step 3 recommendation for children aged under 5 in the British Asthma Guideline is not a LABA.
- LABAs are widely used in COPD and this meta-analysis only covers asthma. However, the authors of this study, in the discussion section, highlight another meta-analysis covering COPD and report that inhaled anticholinergics reduced respiratory deaths by 70% while beta-agonists increased respiratory deaths by more than 2-fold compared to placebo.

1. N Engl J Med 2005; 353: 2637-9 2. Lancet 2006; 367: 286-8 3. Ann Intern Med 2006; 144: 904-12 4. Ann Intern Med 2006; 144: 936-7