General Practice Airways Group

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Dear Alana,

ICS and LABAs for the treatment of chronic asthma in adults and children aged 12 years and over: Systematic review and economic analysis

The preparation of this report has clearly been a mammoth task into which a huge amount of painstaking and methodical work has been put. Within the limited scope of the appraisal and with the limited amount of economic data available, the conclusions appear fair.

We would like to make the following specific comments:

The Title of the Appraisal "ICS and LABA's for the treatment of Chronic Asthma …..Systematic Review and economic analysis" is misleading.

- The review does not deal with a systematic review of LABAs , only with their interaction with ICS.
- The "systematic review" of ICS suggests that all clinically important aspects will be dealt with. In fact there are some notable omissions in the assessment such as the long term safety/side effects of ICS and the dose-response of ICS (see below) and the review is limited to comparisons between drugs.

While we appreciate that you have used the approved title of the appraisals, a more accurate title would be "A systematic review and economic analysis of the comparative effectiveness of different types of ICS and their usage with LABA's"

Methodology:

1. It is a shame that the scope of the appraisal does not include the clinically important questions of :a) the dose-response (or lack of it) of inhaled steroids . This is important in view of the clinical and economic impact of the widespread practice of inappropriately high doses of inhaled steroids. The authors state, in the body of the text, that this issue is dealt with in a previous Cochrane review, but in view of its clinical and economic importance, it should really have been included in a "systematic review and economic analysis of ICS" commissioned by NICE.

2. Similarly the lack of inclusion of long term safety/side effect observational studies has left a large gap in the safety data which one would assume in the title of "a systematic review of ICS and LABA"

3. As acknowledged by the authors, the paucity of real cost-effectiveness data has lead to the economic analysis being carried out on a cost-minimisation basis i.e which is the cheapest drug. We fear that the discussion in the text about "real world issues" of lack of compliance due to lack of tolerability or an inhaler device that isn't used properly will be lost by the headline message that comes over in the assessment about which is the cheapest drug, based on the artificial asthma patient base of the Randomised Controlled Trial.

4. It is recognized in the 'background' section that inhaled delivery systems may have a significant effect on outcomes, but it is said that this lies outside the remit of this evaluation. The choice of device is of great importance to us as community practitioners, and we feel it is unfortunate that this important aspect of the use of these technologies is omitted. Many of the technologies considered are available only through one system, and in practice, community practitioners tend not to separate the choice of drug from the choice of device. We would expect that any guidance would acknowledge that decisions on compound are inextricably linked to decisions about the device in the headline recommendations, not just buried in the body of the report.

Specific Points:
Background Section.
3.1.4.
It is stated that "most exacerbations can be treated with high doses of inhaled SABA's although sometimes a short course of oral steroids is needed".
The BTS/SIGN Guidelines emphasise the value of personal asthma action plans in which the dose of inhaled steroid also needs to be increased.
3.5
This deals with a list of outcome measures. A notable absentee in the list of measures is the Asthma Control Questionnaire (ACQ-Juniper) which has been recommended by the American Thoracic Society/European Respiratory Society (ATS/ERS) joint asthma task force as a major outcome measure in clinical trials.

Clinical effectiveness section
5.1.2.2
It is a shame that, at a time of transition from CFC to HFA BDP inhalers that the assessment does not address the clinical effectiveness (especially the claims made regarding 1:1 or 1:2 dosing ratio) between the CFC and HFA preparations of BDP.

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While we appreciate that this assessment report is necessarily based on a lot of data on CFC-containing inhalers, care needs to be taken that the final guidance issued to the NHS is appropriate. It would not be helpful for the guidance to state that CFC-driven BDP inhalers are the treatment of choice just as they are to be withdrawn. The worst case scenario would be that a clinician is encouraged by NICE guidance to initiate a CFC- containing form of BDP, for example, and then have to switch the patient again once this form of BDP is discontinued. We know that GlaxoSmithKline plan to discontinue Becotide and Becloforte (both CFC-containing forms of BDP) in September 2007, and we believe, though cannot confirm, that a considerable amount of corticosteroid prescribing is in these brands. We would recommend that NICE talks with relevant individuals at the Department of Health and the Department for Environment Food and Rural Affairs who are overseeing the phasing out of CFCs in line with the Montreal Protocol, in order to ensure compatible timing and messages.

At present the focus in the Assessment report is on the current situation with CFC-containing inhalers being available, but alluding to a future change. It may be better to focus the key recommendations in the Final Appraisal Determination (FAD) on the future situation in the knowledge that CFC-containing inhalers are in the process of being discontinued. It is important that NICE issues guidance that is timely and appropriate, and that causes the least disruption to continuity of patient care. For your information, we have attached the Opinion sheet that GPIAG has prepared for primary care health professionals on the topic of CFC discontinuations, which can be found on our website. A relevant extract is as follows:

> The disadvantage of explicitly prescribing a CFC-containing beclomatasone inhaler now is that a further change will be necessary when all CFC-containing MDIs become unavailable. Changing now is also better for the ozone layer!

5.7.1

It is stated that “the mean adjusted exacerbation rate of the third trial (Volgemeier C et al European Respiratory Journal 26: 819-828 2005) was lower in the SALM:FP group than in the BUD;FF group. This led to one of the conclusions in the summary of this section that effectiveness of the one combination versus the other was variable across all endpoints.

In fact in the Volgemeier study, the mean exacerbation rate per patient was lower in the BUD/FF group than in the FP/SALM group (0.24v 0.31 exacerbations per patient per year) in line with the other 2 comparative studies showing that adjustable therapy with BUD/FF is superior to SALM/FP in terms of exacerbations. The conclusion stated in the text is therefore incorrect.

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Conclusions

Section 9.1

This section advocates the use of patient-centred outcome measures (such as Quality of Life) in future research. This is very much welcomed. Much of the analysis has been based on studies where the primary endpoint has had little meaning in the day to day asthma clinic (e.g. Mean morning peak flow). This has proved to be a particular problem where an economic analysis is attempted. There is a paucity of data with economically quantifiable endpoints such as number of exacerbations / hospitalisations or Quality of Life data.

The randomized controlled trails have been largely carried out on patients who have to fulfil very strict entry criteria (such as reversibility of lung function with beta agonist >12%), drawn from secondary care and who therefore do not represent the bulk of asthma patients seen in primary care

We hope that NICE will acknowledge this particular limitation of the Assessment Report in translating the findings to recommendations in the Appraisal Consultation Document and Final Appraisal Determination regarding use of ICS in everyday clinical practice . We reiterate the recognition by the authors of this assessment report regarding patient –centred outcomes and hope that NICE will be encouraged to look outside the often artificial world of the RCT in future assessments.

The GPIAG are keen to continue working with you to ensure that the best possible guidance is developed on the use of inhaled steroids in asthma management. Please contact me if you have any further queries.

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Opinion

GPIAG Opinion Nº 9

Discontinuation of CFC-containing beclometasone metered dose inhalers - planning for change

Introduction
Inhaled corticosteroids are the key to successful management of persistent asthma symptoms, and are also used in the management of patients with chronic obstructive pulmonary disease (COPD). Many patients continue to use beclometasone dipropionate by metered dose inhaler (MDI). CFC propellants in MDIs are harmful to the environment and their supply is being phased out worldwide under the terms of the Montreal protocol. A new milestone has been reached in this process with the launch of a second CFC-free formulation of beclometasone - Clenil® Modulite® - in addition to Qvar® which has been available for some time. All CFC-containing beclometasone MDIs will eventually be withdrawn, but Allen and Hanburys/GSK have announced that Becotide and Becloforte MDIs will cease to be available in September 2007. A date for phasing out all CFC-containing beclometasone inhalers has not yet been fixed, but this will eventually occur, and other manufacturers may cease production in advance of this requirement. Environmental considerations favour an early transition to the use of CFC-free inhalers. We might as well get on with it.

The two available CFC-free beclometasone preparations have differing lung deposition: Clenil® Modulite® is equipotent with CFC-MDI beclometasone and the dosage is therefore the same; however, Qvar® is twice as potent due to smaller particle size and therefore the dosage should be halved when converting from CFC-MDI.

MHRA Advice
The MHRA wrote to all doctors and pharmacists in August 2006 advising that doctors should therefore prescribe CFC-free beclometasone inhalers by brand name.[1] Pharmacists are advised to check any generic prescription for beclometasone, to see whether or not a CFC-free product is required. This recommendation means that prescribers will save time and trouble by making appopriate alterations to repeat prescriptions for generic beclometasone as soon as possible.

Managing the transition for patients
Patients currently receiving CFC-MDI beclometasone should be advised of the transition to CFC-free beclometasone when they consult at the practice or when ordering repeat prescriptions, and a plan should be made for continuing treatment.

For patients with asthma the opportunity should be taken to review disease control so that any step up or down in the dosage of inhaled steroid and other agents can be implemented if necessary. The RCP 3 questions[2] or the GPIAG/Allergy UK Asthma Assessment Tool[3] may be used to assess asthma control.

Problems with inhaler technique and adherence should be carefully assessed before deciding on the need for any change in inhaled steroid dosage.

Management should be staged according to agreed guidelines,[2] with long-acting beta-agonists (LABAs) being used in preference to an increase in the daily inhaled steroid dosage above 800mcg beclometasone equivalent in adults or 400mcg in children. Combination inhalers should be considered for patients demonstrating a continued long-term requirement for both ICS and LABA.

CFC-free inhalers may taste and "feel" differently compared to the patient's previous CFC-containing inhaler, and patients should be advised about this - although many patients will already be familiar with these issues following the switch to CFC-free salbutamol.

Good asthma control
For patients whose asthma is generally well controlled on CFC-MDI beclometasone, a CFC-free alternative can be prescribed by brand name - either at equivalent dosage (Clenil®Modulite®) or at half the previous beclometasone dosage (Qvar®). Qvar®is not licensed for children under 12 years of age. If the patient uses a spacer the recommended product is the Volumatic® for Clenil® and the Aerochamber® for Qvar®· Clenil® Modulite® is available as an MDI, while Qvar® is available in a range of inhaler types (MDI, Autohaler, Easi-breathe).

The disadvantage of explicitly prescribing a CFC-containing beclomatasone inhaler now is that a further change will be necessary when all CFC-containing MDIs become unavailable. Changing now is also better for the ozone layer!

Remember that if asthma control is really good a step down in inhaled steroid dosage should be considered. BTS/SIGN guidelines emphasise the importance of titrating inhaled steroid dosage down to the lowest dose that provides good symptom control.

Poor asthma control
If asthma control is poor:

- Undertake a full clinical assessment checking adherence and inhaler technique including spacer use, exploring allergic triggers, checking for rhinitis and revisiting the diagnosis if necessary.
- Consider the treatment options
  - ~ addition of a further therapeutic agent such as an LABA
  - ~ maintaining or increasing the dose of inhaled steroid by prescribing a CFC-free beclometasone formulation by brand name - as above.
  - ~ changing to an alternative inhaler type or therapeutic agent; alternative inhaled steroids are budesonide, ciclesonide, fluticasone and mometasone.

Changes of inhaler type or therapeutic agent may have significant cost

implications. The clinical effectiveness of different inhaler types for any particular steroid agent and dosage is broadly similar.[4] Factors influencing choice of inhaler type include the availability of the drug/device combination, the patient's ability and willingness to use the device and the cost of treatment. Fluticasone, like Qvar®, should be prescribed at half the intended beclometasone dose and ciclesonide at about ¾ of this dose. Estimated daily equipotent doses of inhaled steroids are available on the GINA guidelines at http://www.ginasthma.org, see Fig 3.1, page 29 and Fig 3.4, page 46 for adults and children respectively.

After any change in asthma treatment, patients should be monitored closely, ideally using peak flow diaries, and offered early review if they experience problems according to self-management plans.

COPD

For patients with COPD, current UK treatment guidelines recommend use of inhaled steroids for patients with an FEV_1 less than 50% predicted suffering two or more exacerbations per year.[5] When consulting with COPD patients to discuss a change to the type of steroid inhaler being prescribed for them, there should also be a thorough clinical review - to check inhaler technique and to consider suggesting use of a spacer.

Current bronchodilator therapy should also be reviewed to ensure that symptomatic benefit has been maximised with a trial of LABA for persistent symptoms. Strictly speaking, inhaled corticosteroids are currently only licensed for use in COPD in combination with an LABA, though in practice many patients continue to use separate inhalers for their inhaled steroid treatment.

Planning for the change in practice

There are three possible approaches to the CFC-free beclometasone transition:

- Opportunistic - change patients' prescriptions as they attend routinely
- Invitation for review - ask patients to come in to the practice
- Managed change - inform patients by letter of the change, offer a review but alter their repeat prescriptions.

The approach taken in general practice will be influenced by a number of factors including the number of patients being treated with beclometasone MDIs, since it is preferable to make the change at the time of a face-to-face consultation.

Notices in the waiting room and in local pharmacies can be used to advise patients who use beclometasone MDIs to discuss the eventual need for change with their doctor or asthma nurse at the next routine visit, or to invite earlier attendance. Similar notices may be printed on computer prescription side-slips

Ensure that all clinical staff who see asthma and COPD patients are aware of these issues, and adopt a consistent approach to the transition. Inform practice reception staff - in particular emphasising the non-urgent nature of the change and the fact that CFC-containing inhalers are perfectly safe but less environmentally friendly.

Discuss the practice's plans for transition with local pharmacists, who can play a key role in advising and informing patients about the change, whether or not this is part of a formal Medicines Use Review (MUR) under the new pharmacy contract.

Ensure patients are given the time they need to understand the reasons for the change; we know that many patients with asthma feel that they do not receive adequate explanation about their treatment. Produce or provide written patient information materials. Asthma UK have produced an excellent patient information leaflet for patients available at http://www.asthma.org.uk/document.rm?id=224

Impact on prescribing costs

Cost differences between CFC-free and CFC-containing beclometasone MDIs are small, with the exception that Becotide® - which is now being phased out - has for some time been significantly less expensive than other preparations. There will therefore be some unavoidable increased prescribing costs with the transition to CFC-free beclometasone - from about £26 to about £56 per patient for a year's treatment at 400mcg per day of CFC-beclometasone equivalent when comparing with the cost of Becotide®. Costs are similar, though at the time of writing Clenil® is slightly cheaper than QVAR® (source BNF).

Conclusion

The transition to CFC-free metered dose inhalers for bronchodilators took place with much less difficulty than forecast, and prior experience with this transition will help patients and practices in dealing with the same change for beclometasone MDIs. It is important for patients and practitioners to be aware of the need for dose reduction if switching to Qvar® and hence the requirement that CFC-free beclometasone inhalers should be prescribed by brand name. There is no reason why this change should in itself necessitate a reduction in the use of beclometasone which remains an effective treatment for asthma with an excellent safety record when prescribed with the proper precautions.[6,7] We should use the transition process to review and optimise the control of patients' symptoms - a process which will also contribute to achieving QOF targets in asthma and COPD.

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