

Meta-Review: Adverse Effects of Inhaled Corticosteroids Relevant to Older Patients

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Published online: 22 March 2014
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Abstract

Background In recent years, clinical trials and observational studies have raised concerns about the potential adverse effects of inhaled corticosteroids (ICS) such as pneumonia, cataract, fractures and hyperglycaemia, which are of particular concern for older patients.

Methods We conducted a meta-review by searching electronic databases (MEDLINE, EMBASE, PubMed) for systematic reviews and meta-analyses of ICS use and the adverse effects of interest. We also evaluated new primary studies that reported information beyond that available from previously published meta-analyses. Two reviewers independently extracted data on measures of associated harm with ICS use.

Results We identified five relevant meta-analyses for inclusion in this meta-review, and also three new studies of ICS and pneumonia. We found consistent evidence of a dose–response relationship between ICS use and serious adverse effects such as fractures and pneumonia. The estimated number needed to treat for harm due to fracture with ICS was 83 with 3-years use, and 60 per year for pneumonia. Both asthma and chronic obstructive pulmonary disease (COPD) users of ICS were at risk of pneumonia, with fluticasone appearing to confer higher risk than budesonide. There is also some suggestion that ICS use is associated with cataracts in a dose–response manner but

the evidence is less robust here. Equally, the influence of ICS on diabetes mellitus remains uncertain.

Conclusions In view of the dose–response relationship seen between ICS use and important adverse effects such as fractures and pneumonia, clinicians needs to carefully balance the benefits of ICS versus the harms in older patients receiving long-term high-dose ICS.

Key Messages

There is an increased risk of pneumonia with inhaled corticosteroid (ICS) use in chronic obstructive pulmonary disease (COPD) and asthma patients, with fluticasone carrying a greater risk

ICS also increase the risk of fractures in a dose-responsive manner

While we found some evidence of increased risk of cataract there was no definite association with new-onset diabetes mellitus

Electronic supplementary material The online version of this article (doi:10.1007/s40265-014-0202-z) contains supplementary material, which is available to authorized users.

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1 Introduction

Inhaled corticosteroids (ICS) are widely used in the treatment of obstructive airway disease, including asthma and chronic obstructive pulmonary disease (COPD). Currently, up to 70 % of patients with COPD are prescribed an ICS [1]. The National Institute for Health and Care Excellence (NICE) in the UK recommends that patients with COPD who remain breathless or have exacerbations despite the use of a short-acting β -agonist (SABA) ought to be offered a long-acting β -agonist (LABA) with ICS in combination if their forced expiratory volume in 1 second (FEV₁) is

<50 % predicted [1]. Unlike asthma, where the role of ICS is well established, there is little evidence that an ICS alone is of benefit in patients with COPD, and their role in improving COPD symptoms is unproven [2].

Prior to the completion of a large, long-term, randomised controlled trial (RCT) in 2007, ICS were considered to be relatively free from serious side effects, although cataracts and hyperglycaemia have been considered as potential problems [3]. However, recent RCTs and meta-analyses have raised concerns regarding more severe adverse effects such as pneumonia and fractures [4, 5]. Both patients and physicians are concerned about potential side effects and how to balance this against the benefits of using ICS. This is a particular problem in elderly patients who have multiple co-morbidities, particularly with underlying cardiac, respiratory and bone disease where drug-induced pneumonia or fractures could lead to substantial morbidity or even mortality. Any additional burden from drug-induced harm would be of serious concern here, given that older people have a background rate of approximately 25–44 cases of community-acquired pneumonia per 1,000 persons, rising to as high as 52 per 1,000 persons in those aged 85 years or over [6]. Equally, fractures have been recognised as a growing public health problem due to their increasing incidence in the ageing population, with Bliuc et al. [7] reporting an average fracture incidence of 32 per 1,000 person-years in women and 17 per 1,000 person-years in men.

Hence, our objective was to evaluate and critically appraise up-to-date evidence regarding the risk of ICS use in COPD patients, so that practitioners and patients can make informed decisions and optimise the management of COPD. We chose to focus on fractures, pneumonia, cataracts and hyperglycaemia because these are of particular relevance to older patients. As there are already several recent systematic reviews addressing these topics, we aimed to perform a meta-review (overview summarising the most recent systematic reviews). If there were no systematic reviews covering the specific adverse effect or the systematic review was potentially outdated, we planned to summarise the findings of relevant primary studies.

2 Methods

2.1 Study Selection Criteria

We included systematic reviews and meta-analyses of ICS that aimed to evaluate specific adverse effects of interest using defined methodology:

- reproducible search strategy
- explicit study selection criteria

- synthesised data in a meta-analysis

If there were several systematic reviews available, we chose to summarise the findings from the most recent one.

We included primary studies that satisfied the following criteria:

RCT or controlled observational study with the main aim of specifically assessing the adverse effect of interest in participants receiving ICS as compared with controls not treated with ICS.

2.2 Search Strategy

Full details of the search strings are listed in Appendix 1 (see electronic supplementary material). In brief, we used the systematic reviews filter on PubMed to identify relevant articles on ICS and we also ran separate searches in EMBASE, MEDLINE and PubMed Automated Updates to identify other potentially relevant articles.

2.3 Data Extraction

Systematic reviews were extracted by one reviewer and checked by a second, while primary studies were independently extracted by two reviewers. The reviewers extracted data on to pre-formatted tables regarding characteristics of the study, type of participants, and results of the meta-analyses where odds ratio (OR), relative risk (RR) or number needed to treat for harm (NNTH) were described. In view of the differences in relative potencies of different ICS agents [8], we extracted data (where available) on dosages based on beclomethasone dipropionate equivalents. Both reviewers met to discuss and reach final consensus on the extracted data.

2.4 Validity Assessment

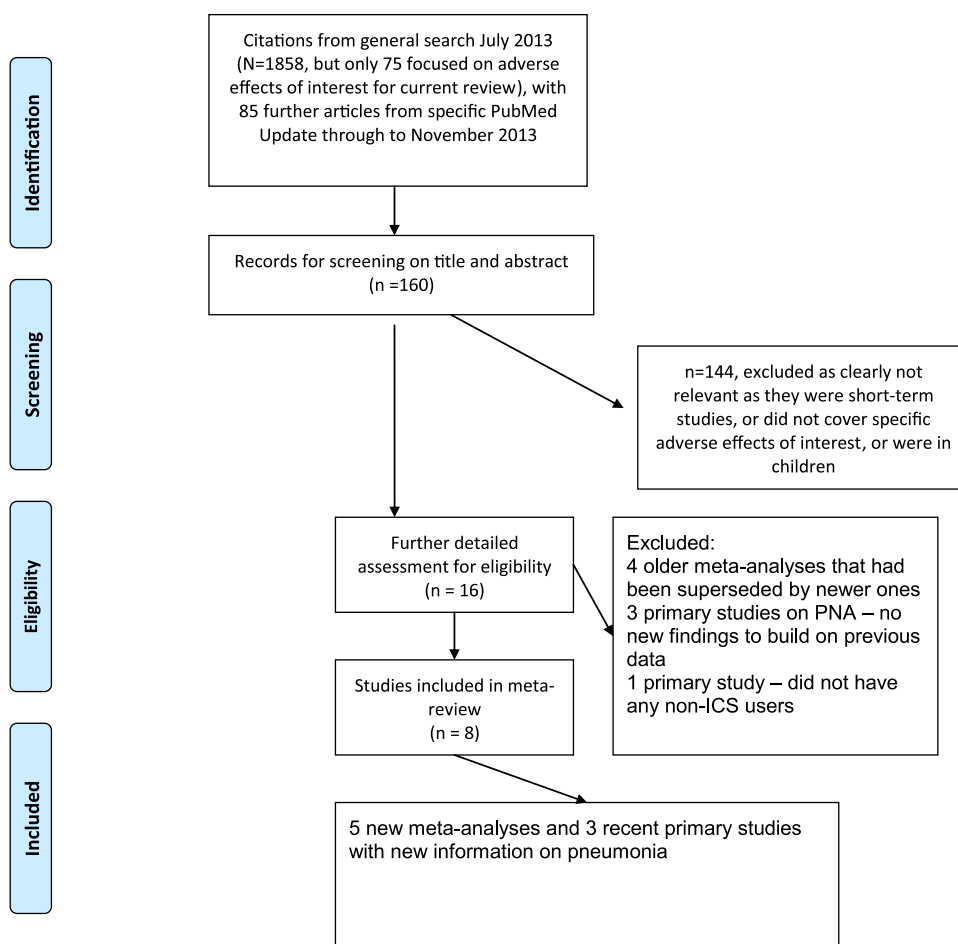
For systematic reviews, we recorded the search strategy, how many studies were included, type of study designs included, and extent of heterogeneity in the meta-analysis.

For primary studies we recorded ascertainment of outcomes, ICS use and any possibility of confounding.

3 Results

The process of study selection is shown in Fig. 1. We identified five relevant meta-analyses for inclusion in this meta-review [5, 9–12], and also three recent primary studies of ICS and pneumonia with important new information that builds on the findings of the earlier meta-analyses [13–15]. Table 1 summarises the methodological features and key findings of the five included meta-

Fig. 1 Flow diagram of study selection. ICS inhaled corticosteroids



analyses. The characteristics of the new primary studies are listed in Table 2, while assessment of study validity and results are shown in Table 3.

3.1 Effect of Inhaled Corticosteroids on Fractures

We identified two relevant meta-analyses that evaluated ICS and fractures, albeit with differences in type of fracture and the nature of the included studies [5, 12].

The first meta-analysis, conducted by Weatherall et al. [12], was designed to focus primarily on determining the dose–response relationship between ICS use and associated risk of fractures. The authors covered a wide range of patients with obstructive airways disease (including asthma and COPD) but looked only at non-vertebral fractures, and reported that the RR increased by about 12 % for each 1,000- μ g (beclomethasone dipropionate equivalents) increase in the daily dose of ICS. However, the meta-analysis was afflicted by substantial heterogeneity and use of a random effects model yielded results that were not statistically significant. There were only five case–control studies in the meta-analysis and the authors were unable to conduct detailed subgroup analysis to examine the

substantial heterogeneity. Moreover, two of the case–control studies included in the meta-analysis were based on participants from the same database, from a similar time period. The meta-analysis did not differentiate between fracture type and site amongst the non-vertebral fractures, which is a further limitation.

In contrast, Loke et al. [5] considered both randomised and non-randomised study designs in their meta-analysis of 16 RCTs and seven observational studies. This meta-analysis evaluated all fracture types rather than just non-vertebral events, and found that ICS use was consistently associated with a statistically significant increase in the risk of fractures in patients with COPD, with an estimated NNTH of 83 over 3 years of ICS use. The dose–response relationship yielded findings of similar magnitude to Weatherall et al. [12], with each 500- μ g increase in beclomethasone dose equivalents being associated with a 9 % increase in risk of fractures. However, the overall effect size was modest (Peto OR 1.27; 95 % CI 1.01–1.58). The lower boundary of the confidence intervals lies close to the null effect, thus introducing some uncertainty. Other limitations are that there were no uniform methods of defining, recording and classifying fractures according to

Table 1 Characteristics and results of meta-analyses reporting on risk of adverse effects with inhaled corticosteroids

References	Search date	Databases searched	Drug use	Other inclusion criteria	Definition of adverse event	Extraction methods	Results
Singh and Loke [10]	Initial search up to 30 June 2008, updated 2010	PubMed, EMBASE, Cochrane Database of Systematic reviews, manufacturer and regulatory authorities websites, Web of Science	ICS use in COPD	RCTs, observational studies Mean age of patients 59–67.5 years	Pneumonia, serious pneumonia (reported as hospitalisation, disability, death)	Independent screening and extraction by 2 reviewers	Risk of pneumonia with ICS use: 24 RCTs ($n = 16$ fluticasone, 7 budesonide, 1 mometasone) RR 1.56; 95 % CI 1.40–1.74, $p < 0.0001$, $I^2 = 15$ % Observational studies RR 1.44; 95 % CI 1.20–1.75, $p = 0.0001$ NNTH for pneumonia associated with ICS use from trial data: 60 (95 % CI 44–84)
Weatherall et al. [12]	Up to January 2007	Medline, EMBASE	ICS use in asthma, COPD and other chronic respiratory conditions	Case-control studies that reported on fracture risk according to dose Adults	Non vertebral fracture	Not reported	Five case-control studies of beclomethasone or budesonide users: non-vertebral fracture per 1,000 mcg dose increase (beclomethasone dipropionate or equivalent) Fixed effects OR 1.08; 95 % CI 1.03–1.12. Random effects OR 1.12; 95 % CI 1.00–1.26; $I^2 = 79$ %
Loke et al. [5]	Initial search up to April 2009, updated August 2010	MEDLINE, EMBASE, manufacturer and regulatory authorities websites, Cochrane Systematic Reviews	ICS use in COPD (RCTs), and in obstructive airways disease (observational studies)	RCTs (budesonide or fluticasone for COPD >24-weeks duration) Observational studies (ICS exposure vs no exposure) Mean age of patients 52–65.9 years	Fracture	Independent screening and extraction by 2 reviewers	16 RCTs (14 fluticasone, 2 budesonide) Peto OR 1.27; 95 % CI 1.01–1.58; $p = 0.04$; $I^2 = 0$ % Observational studies: OR 1.21; 95 % CI 1.12–1.32; $p = <0.001$; $I^2 = 37$ % Each 500-µg increase in beclomethasone dose equivalents associated with a 9 % increased likelihood of fractures: OR 1.09; 95 % CI 1.06–1.12, $p \leq 0.001$
Weatherall et al. [11]	1950–2007	MEDLINE, EMBASE, reference lists of relevant studies	ICS use in COPD and asthma	4 Case-control studies	Cataract	Independent screening and extraction by 2 reviewers	Significant relationship between risk of cataract and ICS dose Random effects pooled OR 1.25 for risk of cataract per 100-µg increase in daily beclomethasone dose 95 % CI 1.14–1.37, $I^2 = 65.5$ % Fixed effects OR 1.20; 95 % CI 1.16–1.24
O'Byrne et al. [9]	Completed trials as of December 2010	Astra Zeneca manufacturer's trial data	Budesonide alone or budesonide/formoterol combination in COPD and asthma	Double-blind RCTs, patients >4 years of age with either asthma or COPD, follow-up of >3 months (asthma) or >6 months (COPD)	Diabetes mellitus or hyperglycaemia coded as AE or SAE in the RCT	Not stated	Risk of diabetes or hyperglycaemia: for asthma, 26 RCTs; RR 1.02; 95 % CI 0.42–2.53 for COPD, 8 RCTs; (RR 0.94; 95 % CI 0.65–1.37)

AE adverse event, COPD chronic obstructive pulmonary disease, ICS inhaled corticosteroids, NNTH number needed to treat for harm, OR odds ratio, RCTs randomised controlled trials, RR relative risk, SAE serious adverse event

Table 2 Characteristics of primary studies reporting on pneumonia with inhaled corticosteroids

References	Design	Adverse effects measured	Data source and number of patients	Selection of patients: definition and patient characteristics (or selection of cases and controls)	Type of ICS
Eurich et al. [13]	Nested case control	Recurrent pneumonia	Edmonton prospective clinical registry, secondary care 2000–2002; 653 cases/6,244 controls	Age >65 years, with community-acquired pneumonia treated in secondary care Cases: recurrent pneumonia ≥30 days after initial episode Controls: matched on age, sex and COPD; no recurrence of pneumonia Mean age 79 years, 52 % male Indication for ICS use not recorded	Beclomethasone, fluticasone, or budesonide
McKeever et al. [14]	Case control	Pneumonia/LRTI	Primary care (Health Improvement Network) database; April 2004–; 6,857 cases; 36,312 controls	Age 18–80 years, diagnosis of asthma (COPD excluded) Cases: Read codes for first recorded diagnosis of pneumonia or LRTI Controls: age and sex matched, no pneumonia Mean age 54 years, 39 % male	Beclomethasone dipropionate, fluticasone propionate, budesonide, combined group of ciclesonide and mometasone furoate
Suissa et al. [15]	Nested case control	Severe pneumonia (first hospitalisation for or death from pneumonia)	Quebec health insurance databases 1990–2005; 20,344 cases/197,705 controls	Age >55 years, new users with ≥1 prescription for bronchodilator or ICS and no previous use in preceding 2 years. No verification of COPD diagnosis but patients with asthma excluded Cases: ICD codes for hospitalisation for or death from pneumonia Controls: age and time matched, no pneumonia	Beclomethasone, fluticasone, budesonide, triamcinolone and flunisolide

COPD chronic obstructive pulmonary disease, *ICD* international classification of diseases, *ICS* inhaled corticosteroids, *LRTI* lower respiratory tract infection

type and relationship with duration of ICS use. There were no long-term trials looking at budesonide versus fluticasone propionate in COPD, and no conclusions could be drawn on effect of different corticosteroid preparations.

3.2 Cataract

We identified a meta-analysis by Weatherall et al. [11] that demonstrated an approximately 25 % elevation in the risk of cataract for each 1,000-μg per-day increase in the dose of beclomethasone equivalents. However, there were only four observational studies included in this meta-analysis, with potential overlap in the analysis because the participants came from similar databases (General Practice Research Database, UK for two studies, and Canadian health insurance database for two studies). Weatherall et al. mention the possibility that the pairs of studies using the same patient databases may therefore not have generated independent estimates for pooling within the meta-analysis. Equally, one major primary study was excluded because

Weatherall et al. used an analytical method that did not match the data format presented in the primary study. Moreover, there was no differentiation of the different types/anatomical sites of cataract, thus making it difficult for readers to assess the clinical or functional importance in patients. The case–control design of the included studies also made it difficult to judge absolute rates of harm, and, as such, there was no mention of clinically meaningful measures such as NNTH.

3.3 Diabetes Mellitus

We identified a meta-analysis that was based on all the trials of inhaled budesonide within the manufacturer's database [9]. The authors looked at double-blind RCTs (26 for ICS use in asthma and 8 for ICS use in COPD) and assessed the number of adverse events (recorded through spontaneous reporting systems) related to diabetes mellitus or hyperglycaemia. It did not identify an increased risk of new onset diabetes mellitus or hyperglycaemia. However,

Table 3 Study validity and results of primary studies reporting on pneumonia with inhaled corticosteroids

References	Outcome; ascertainment and validation of adverse effect	Definition of ICS use; verification of actual exposure; follow-up period or study duration	Statistical adjustments for confounding factors (if any)	Results (risk of adverse effect with ICS use)
Eurich et al. [13]	ICD codes (98 % sensitivity and 97 % specificity) for hospitalisations or emergency department visit with pneumonia No radiographic confirmation	Dispensing of prescriptions: Current use: dispensed within 90 days; past use: >90 days; non-users if ICS use in week prior to pneumonia event and no previous ICS dispensations No exposure verification	Age, sex, comorbidities, smoking, premorbid functional status, nursing home residence, vaccinations, prescription medicines and pneumonia severity	Adjusted OR recurrent pneumonia: Current use: 1.90 (95 % 1.45–2.50), NNTH 20 Past use: 1.15 (95 % 0.85–1.55) Incident current use: 1.85 (95 % 1.37–2.50) COPD: 1.72 (95 % 1.17–2.55) No COPD: 2.31 (95 % 1.53–3.49)
McKeever et al. [14]	Read codes No radiographic confirmation	Prescriptions issued: Current use: within 90 days of index date No exposure verification	Age, sex, smoking; Charlson Comorbidity Index; influenza vaccination; reliever inhalers and oral corticosteroids in previous year, Townsend socio-economic status score	Adjusted OR pneumonia: Overall current: 1.24 (95 % CI 1.15–1.33) Age <40 years, no bronchiectasis: 1.24 (95 % CI 1.07–1.44) Steroid formulation: fluticasone 1.64 (95 % CI 1.50–1.79); budesonide 1.20 (95 % CI 1.06–1.35) Non-significant findings for other ICS
Suissa et al. [15]	Quebec hospitalisation database (ICD codes for pneumonia). For outpatients, pneumonia as principal cause of death No mention of radiographic confirmation	Dispensing of outpatient prescriptions: Current use: dispensed within 60 days; non-users if no prescription within past year Mean follow-up 5.4 years No exposure verification	Age, sex, severity of respiratory disease (proxy measure of respiratory drugs and hospitalisation for COPD), and co-morbidities associated with pneumonia (proxy measure of drug use for other diseases)	Adjusted RR for severe pneumonia: Current users: 1.69 (95 % CI 1.63–1.75) Fluticasone: 2.01 (95 % 1.93–2.10) Budesonide: 1.17 (95 % 1.09–1.26)

CI confidence interval, COPD chronic obstructive pulmonary disease, ICD international classification of diseases, ICS inhaled corticosteroids, NNTH number needed to treat for harm, OR odds ratio, RR relative risk

as this meta-analysis relied on spontaneous adverse event reports in short-term clinical trials, there was no formal biochemical validation of diabetes and the patients included in the studies did not generally have significant comorbidities. Hence, there is a considerable degree of imprecision in the estimates, particularly in the analysis where the authors compared budesonide with fluticasone.

3.4 Pneumonia

We found one meta-analysis by Singh and Loke [4, 10] (which is an update of an earlier analysis by the same authors [4, 10]), and three new primary studies reporting on pneumonia with ICS which were not part of the meta-analysis [13–15].

This updated meta-analysis demonstrated a significantly increased risk of pneumonia in patients with COPD (RR 1.56, 95 % CI 1.40–1.74) with ICS therapy in pooled data from long-term RCTs of fluticasone propionate, budesonide and mometasone [10]. The NNTH for pneumonia associated with ICS was estimated to be 60 per year. However, owing to the lack of long-term head-to-head trials between different ICS formulations, Singh and Loke were not able to draw any conclusions regarding potential differences between formulations. It was also unclear whether continuation of ICS therapy would lead to recurrence of pneumonia, or if ICS users with asthma (rather than COPD) would be faced with a similar risk of pneumonia. Hence, we have included three new primary studies that have addressed these key questions in our meta-review.

Suissa et al. [15] published a nested case–control study in 2013 looking at whether the risk of pneumonia varies with different classes of ICS (particularly looking at budesonide and fluticasone). The study showed that any ICS use in COPD compared with non-use was associated with a significant increase in the risk of serious pneumonia (hospitalisation or death). Although significant risk was seen with both agents (fluticasone or budesonide), the magnitude of risk of serious pneumonia was higher with fluticasone (RR 2.01, 95 % CI 1.93–2.10) than that seen with budesonide (RR 1.17, 95 % CI 1.09–1.26). Overall, the risk declined after stopping ICS use, diminishing below the threshold of statistical significance after 6 months (RR 1.08, 95 % CI 0.99–1.07). Whilst the size of the study (>160,000 patients) is a strength, the fact that there was no mention of radiographic confirmation of the diagnosis has to be a limitation. There was also no exposure verification of the use of ICS.

McKeever et al. [14] looked at the risk of pneumonia in patients with asthma using ICS. Their case–control study showed a dose–response relationship between the dose of ICS and the risk of pneumonia or lower respiratory tract relationship. The adjusted OR for current ICS use was 1.24 (95 % CI 1.15–1.33). This study found a higher risk of pneumonia in patients using fluticasone (OR 1.64, 95 % CI 1.50–1.79) whereas patients using budesonide appeared to have a lower likelihood of harm (OR 1.20, 95 % CI 1.06–1.35). Sensitivity analysis restricted to patients below 40 years of age, or those without bronchiectasis, did not change the findings. However, limitations of this study include absence of radiological confirmation of pneumonia, or exposure verification of actual drug use.

It is worth noting that the studies by Suissa et al. [15] and McKeever et al. [14, 15] both reported greater magnitude of risk for pneumonia with fluticasone than budesonide. Equally, both studies confirmed the presence of a dose–response relationship with higher ICS doses conferring significantly greater associated risk of pneumonia.

Eurich et al. looked at the risk of recurrent pneumonia with ICS use in patients who had survived an initial episode of pneumonia (nested case–control study) [13]. The adjusted OR for recurrent pneumonia in current ICS users was 1.90 (95 % CI 1.45–2.50), with a NNTH of 20. The risk remained elevated even when the analysis was separated into COPD and non-COPD patients. However, there was no spirometric data, radiological confirmation of pneumonia or exposure verification, and the dose of ICS used was not captured by this particular healthcare database. The authors reported that there was insufficient power to capture differences between agents.

4 Discussion/Implications

Our meta-review provides up-to-date evidence regarding the risk of ICS use in asthma and COPD patients. We have identified consistent evidence of a dose–response relationship between ICS use and the associated risk of important adverse effects such as fractures and pneumonia [5, 10, 12, 13, 15]. There is also some suggestion that ICS use is associated with cataracts (a major clinical and public health problem accounting for about half of all cases of blindness worldwide) in a dose–response manner but the observational evidence is less robust here [11]. Equally, the influence of ICS on diabetes mellitus remains uncertain [9]. Our findings should help clinicians direct their attention towards specific key concerns in management of older patients who are on high doses of ICS, bearing in mind that fractures and incident or recurrent pneumonia can pose a substantial threat to patients' health.

Here, we need to consider the balance between benefit and harm in arriving at an appropriate dose, which should be the lowest possible dose that provides adequate symptom relief while minimizing the risk of harm. A number of experts have argued that much of the therapeutic benefit in asthma can be achieved with doses around 400 µg of beclometasone equivalents, and that the trend towards use of higher ICS doses in asthma and COPD may be of some concern [8, 12]. Equally, Singh et al. [10] have pointed out that ICS have only a modest benefit in COPD, and that other therapeutic options should be considered. We believe that clinicians should carefully review the ICS regimen and avoid higher doses unless there has been clear demonstrable benefit, particularly in frail elderly patients who are already susceptible to fractures and pneumonia.

Selection of appropriate patients for initiation of ICS therapy is another key issue. White et al. [2] evaluated the use of ICS in COPD patients within a primary care database, and aimed to determine if ICS therapy was concordant with the recommendations of an international guideline. Around 38 % of patients were judged as 'over-treated' with ICS, and the investigators estimated that there would be an additional 12 cases of pneumonia resulting from inappropriate use of ICS in 897 patients within their dataset. The study concluded that economic costs and clinical harms of ICS should be important considerations, particularly if the benefits are modest or unproven.

Our meta-review also adds important new information on the threat of pneumonia. There is accumulating evidence that ICS use carries an increased risk of pneumonia, both in asthma and COPD, and, as such, clinicians should remain vigilant for respiratory infections in all older patients who are taking ICS, particularly where fluticasone is used. Clinicians and patients may wish to consider differences in benefits and safety profiles when making

decisions on their preferred agents. We also identified new evidence demonstrating that there is a significant risk of recurrent pneumonia if ICS are continued (NNTH of 20), and we believe that the role of continued ICS therapy should be carefully re-evaluated in older patients who are discharged from hospital after an episode of pneumonia. As increasing age is a well established prognostic factor for fatal outcomes in pneumonia [16–18], we are concerned about longer-term pneumonia mortality and morbidity stemming from ICS use in older patients. For instance, Kaplan et al. [19] reported that almost half of the older patients hospitalised with community-acquired pneumonia had subsequently died within a year of discharge from hospital. A recent paper by Davydow et al. [20] also showed that hospitalisation for pneumonia in adults aged over 50 years was associated with subsequent functional decline, cognitive impairment and depressive symptoms. Further research needs to be carried out in relation to the two commonly used ICS (fluticasone/budesonide) as to why they have different effects on the risk of pneumonia, and whether there is any way of reducing these risks.

Our meta-review also identified fairly consistent evidence that ICS therapy carries a higher risk of fractures. We believe the physical and social consequence of fractures to be of particular importance for older patients who may already be frail and poorly mobile. For instance, Bliuc et al. [7] reported that low-trauma fractures in older patients were associated with a near-doubling in mortality rate for 5–10 years after the fracture event. There is clearly a need for more careful use/assessment of ICS therapy in older patients with higher risk of fractures (multiple comorbidities, lower bone mineral density, and recurrent falls). Further research is needed into the precise location of fractures, and the risk of newer ICS formulations needs to be assessed. Studies should also aim to capture a higher proportion of post-menopausal women and compare the available therapeutic options for bone protection in those at risk. This has to be balanced against symptomatic relief and reduction of COPD exacerbations (NNT of 6 to prevent one additional exacerbation) on an individual basis [10].

There is some suggestion of an increased risk of cataracts with high doses and long-term use of ICS [11]. It could be argued that screening for cataracts may be considered for older patients who have been on high doses of ICS for a significant amount of time, although this may already be covered in health services where older patients routinely visit opticians on a regular basis. However, the clinical importance of ICS-related cataracts remain unclear, and further research needs to be carried out regarding the precise anatomical site of cataracts (and the actual influence on visual acuity) and ICS use. Equally, studies to date have not consistently demonstrated an

increased risk of new onset diabetes with ICS use, and we are not certain whether asymptomatic elevations in serum glucose levels confer any substantial worsening in cardiovascular harm in older patients. It is worth noting that Loke et al. [21] conducted a meta-analysis of 23 RCTs and found no difference in risk of myocardial infarction or cardiovascular death in ICS users as compared with non-users. Nevertheless, it would be prudent to re-evaluate the role of high-dose ICS in selected patients who are known to have diabetes mellitus, particularly if glucose control has been problematic.

We are conscious of certain limitations within our findings. Observational studies are subject to confounding, and there are difficulties with the ascertainment of rare, unexpected adverse events (such as pneumonia where radiographic confirmation was not always reported in either the RCTs or the non-randomised studies). Moreover, the generalisability of our meta-review to different geographical regions and extremes of age is uncertain because the studies were typically based in developed countries and were not designed to evaluate very old patients. Although some of the observational studies have attempted to adjust for differences in severity of COPD (through proxy markers such as inhaler or oral corticosteroid use) [14, 15], we recognise that there remains major potential for confounding here. However, it is interesting to note that the effect estimates appear fairly consistent across different populations, and this increases our confidence in the findings when taken together with the dose–response data. Further research needs to also be carried out to evaluate new formulations including mometasone and fluticasone furoate. We believe that it is unlikely that there will be any future head-to-head trials of sufficient sample size to evaluate harm, and as such, large-scale population database studies will be needed to evaluate the comparative safety of these molecules against the existing agents.

5 Conclusions

We have demonstrated a dose–response relationship between ICS therapy and important adverse effects such as fractures and pneumonia. We would advise clinicians and patients to carefully weigh up the benefits of ICS against the harms, particularly with long-term use of high doses of ICS.

Acknowledgments YK Loke and AM Wilson were awarded a grant of £30,000 from Asthma UK charity (AUK-PG-2012-181). K. Mattishent, M. Thavarajah, P. Blanco and D. Gilbert declare no relevant conflicts of interest. The authors designed this study, collected and analysed data, and wrote the manuscript independently of Asthma UK.

References

1. National Clinical Guideline Centre. Chronic obstructive pulmonary disease: management of chronic obstructive pulmonary disease in adults in primary and secondary care, 2010. London; 2010. p. 1–637.
2. White P, Thornton H, Pinnock H, Georgopoulou S, Booth HP. Overtreatment of COPD with inhaled corticosteroids—implications for safety and costs: cross-sectional observational study. *PLoS One*. 2013;8:e75221.
3. Calverley PMA, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *NEJM*. 2007;356:775–89.
4. Singh S, Amin AV, Loke YK. Long-term use of inhaled corticosteroids and the risk of pneumonia in chronic obstructive pulmonary disease: a meta-analysis. *Arch Intern Med*. 2009;169:219–29.
5. Loke YK, Cavallazzi R, Singh S. Risk of fractures with inhaled corticosteroids in COPD: systematic review and meta-analysis of randomised controlled trials and observational studies. *Thorax*. 2011;66:699–708.
6. Faverio P, Aliberti S, Bellelli G, Suigo G, Lonni S, Pesci A, et al. The management of community-acquired pneumonia in the elderly. *Eur J Intern Med*. 2013. doi:10.1016/j.ejim.2013.12.001.
7. Bliuc D, Nguyen ND, Milch VE, Nguyen TV, Eisman JA, Center JR. Mortality risk associated with low-trauma osteoporotic fracture and subsequent fracture in men and women. *JAMA*. 2009;301:513–21.
8. Raissy HH, Kelly HW, Harkins M, Szeffler SJ. Inhaled corticosteroids in lung diseases. *Am J Respir Crit Care Med*. 2013;187:798–803.
9. O'Byrne PM, Rennard S, Gerstein H, Radner F, Peterson S, Lindberg B, et al. Risk of new onset diabetes mellitus in patients with asthma or COPD taking inhaled corticosteroids. *Respir Med*. 2012;106:1487–93.
10. Singh S, Loke YK. An overview of the benefits and drawbacks of inhaled corticosteroids in chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis*. 2010;5:189–95.
11. Weatherall M, Clay J, James K, Perrin K, Shirtcliffe P, Beasley R. Dose-response relationship of inhaled corticosteroids and cataracts: a systematic review and meta-analysis. *Respirology*. 2009;14:983–90.
12. Weatherall M, James K, Clay J, Perrin K, Masoli M, Wijesinghe M, et al. Dose-response relationship for risk of non-vertebral fracture with inhaled corticosteroids. *Clin Exp Allergy*. 2008;38:1451–8.
13. Eurich DT, Lee C, Marrie TJ, Majumdar SR. Inhaled corticosteroids and risk of recurrent pneumonia: a population-based, nested case-control study. *Clin Infect Dis*. 2013;57:1138–44.
14. McKeever T, Harrison TW, Hubbard R, Shaw D. Inhaled corticosteroids and the risk of pneumonia in people with asthma: a case-control study. *Chest*. 2013;144:1788–94.
15. Suissa S, Patenaude V, Lapi F, Ernst P. Inhaled corticosteroids in COPD and the risk of serious pneumonia. *Thorax*. 2013;68:1029–36.
16. Johnstone J, Eurich DT, Majumdar SR, Jin Y, Marrie TJ. Long-term morbidity and mortality after hospitalization with community-acquired pneumonia: a population-based cohort study. *Medicine (Baltimore)*. 2008;87:329–34.
17. Kwok CS, Loke YK, Woo K, Myint PK. Risk prediction models for mortality in community-acquired pneumonia: a systematic review. *Biomed Res Int*. 2013;2013:504136. doi:10.1155/2013/504136.
18. Mortensen EM, Kapoor WN, Chang CC, Fine MJ. Assessment of mortality after long-term follow-up of patients with community-acquired pneumonia. *Clin Infect Dis*. 2003;37:1617–24.
19. Kaplan V, Clermont G, Griffin MF, Kasal J, Watson RS, Linde-Zwirble WT, et al. Pneumonia: still the old man's friend? *Arch Intern Med*. 2003;163:317–23.
20. Davydow DS, Hough CL, Levine DA, Langa KM, Iwashyna TJ. Functional disability, cognitive impairment, and depression after hospitalization for pneumonia. *Am J Med*. 2013;126(615–24):e5.
21. Loke YK, Kwok CS, Singh S. Risk of myocardial infarction and cardiovascular death associated with inhaled corticosteroids in COPD. *Eur Respir J*. 2010;35:1003–21.