Corticosteroids for acute and subacute cough following respiratory tract infection: a systematic review

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Background. Cough associated with acute respiratory tract infection (RTI) is one of the most common problems managed in primary care. Despite minimal evidence for the use of antibiotics, they continue to be prescribed at great cost and are a significant cause of emerging bacterial resistance.

Objectives. To carry out a systematic review of randomized controlled trials to evaluate the effect of corticosteroid therapy in otherwise-healthy adults with acute RTI.

Methods. Seven electronic databases and five ongoing trial registers were searched. Studies were eligible if they compared the use of any corticosteroid treatment against a control group in adults with an acute (<3 weeks) or subacute (<8 weeks) cough associated with an RTI but no asthma. Primary outcomes were differences in mean cough and other symptom scores. Secondary outcomes included adverse effects, subsequent diagnosis of asthma and patient satisfaction.

Results. Four trials (335 participants) investigating the effects of inhaled corticosteroids were identified. None investigated the use of oral corticosteroids. Results were mixed, with two reporting equivalence and two reporting benefits for mean cough score (\(P = 0.012\)) and cough frequency (\(P = 0.047\)). One reported additional benefits in non-smokers. Adverse events were rare and there were no data on patient satisfaction or the subsequent diagnosis of asthma. Most trials were of unclear risk of bias. Study outcomes were too heterogeneous to meta-analyse.

Conclusions. There is sufficient evidence to recommend the routine use of inhaled corticosteroids for acute RTI in adults. However, some trials have shown benefits, suggesting the need for further high-quality, adequately powered trials.

Keywords. Bronchitis, cough, general practice, glucocorticoids, primary health care, respiratory tract infections.

Introduction

Acute and subacute cough, resulting from an acute respiratory tract infection (RTI), is one of the most commonly encountered conditions in primary care.\textsuperscript{1} Lower respiratory tract infection (LRTI) is a self-limiting illness, characterized by cough as the main symptom, along with other symptoms such as wheeze, pain on breathing, sputum production and shortness of breath.\textsuperscript{2} Upper respiratory tract infection, also a self-limiting illness, very frequently leads to a troublesome cough. Although a cough resolving within 3 weeks has been termed acute (and one that persists to 8 weeks termed as subacute),\textsuperscript{3} symptoms can last >3 weeks for a significant proportion of adults with acute infective cough.\textsuperscript{1} Despite the self-limiting nature of RTIs, the cough in particular affects quality of life, disturbs sleep and is one of the most common reasons for work absenteeism.\textsuperscript{5} Even though a wide range of different over-the-counter remedies are available, there is no good evidence that suggests that any of these have a beneficial effect\textsuperscript{5} nor do any prescription-only treatments such as inhaled bronchodilator therapy.\textsuperscript{6} For example, a recent Cochrane review identified only two trials assessing cough expectorants, which did show some benefit, although these trials did not appear adequately powered and were at some risk of bias.\textsuperscript{5} As such, patients continue to attend primary care practitioners in the expectation of an effective prescribed therapy\textsuperscript{7} and are often prescribed an antibiotic. Patients
also often present after the acute illness has settled but the cough remains, posing a management problem for GPs with a lack of treatment options available.

Prescribing antibiotics for RTIs accounts for 60% of all general practice antibiotic prescriptions, and the annual prescribing costs for acute cough alone in the UK exceed £22 million. However, accumulating evidence from the past 2 decades has shown only modest, if any, benefits and these only in the context of significant harms, such as side effects, bacterial resistance, unnecessary use of resources and cost. It is not surprising then that identifying effective alternatives to antibiotics for acute RTI is a priority for the primary care research community and the National Health Service.

LRTI is associated with many symptoms that overlap with asthma, including (in varying combinations) cough, wheeze, shortness of breath and sputum production. Significant inflammatory changes are seen in the airways of both asthmatic and non-asthmatic patients with LRTI, and increased airway resistance is seen in healthy subjects with LRTI compared with healthy subjects without LRTI. Other experimental evidence suggests similar changes to bronchial epithelium in both asthmatics and non-asthmatics during RTI induced by common rhinoviruses, with a significant reduction in forced expiratory volume in 1 second (FEV$_1$) seen in both groups. A Cochrane review did not identify any overall benefit in acute cough in adults with the use of beta-2 agonists, when they might have been expected to work in the presence of bronchial epithelial changes and reduced FEV$_1$. However, the authors do state that within some of the included trials, subgroup analyses suggested an improvement of symptom scores in patients treated with beta-2 agonists compared with patients treated with placebo in whom there was evidence of airflow obstruction. In addition, included trials that showed an overall improvement in the intervention group recruited more patients with a productive cough. Corticosteroids are widely used in the management of airflow obstruction and so would be expected to be of benefit to such a population. Subacute cough following infection is thought to occur because of a transient bronchial hyper-responsiveness. Such hyper-responsiveness is a feature of asthma and is successfully treated with corticosteroids. There is already good evidence that corticosteroids have a role in other RTIs, such as croup in children and acute sore throat in adults.

Although little is known about the role of corticosteroids in acute infective cough in non-asthmatics, they are being used by some European GPs. Both acute and persistent cough following an acute infection are recognized as major problems by both GPs and patients, and at present, there has been no identified effective treatment. There is an urgent need to identify novel therapeutic measures to deal with this common condition, particularly in light of growing patient expectations and growing microbial resistance. Therefore, the aim of this systematic review is to evaluate the effect of corticosteroid therapy in otherwise-healthy adults with acute or subacute cough in the absence of asthma.

Methods

Search strategy

We searched the following electronic databases: the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library; Medical Literature Analysis and Retrieval System Online (MEDLINE; from January 1946 to December 2012); EMBASE (from January 1974 to December 2012); Latin American and Caribbean Health Science Information Database (LILACS; from January 1982 to December 2012); PubMed; and Web Of Science, using a combination of free text words and medical subject headings (MeSH) terms. Full details of search terms are available from the authors on request. Bibliographies of identified studies were also searched. All search terms used were in English; however, citations identified as potentially relevant were not excluded on the basis of language. Searches were last performed in February 2013.

Ongoing trials from the following databases were searched: the metaRegister of controlled trials (www.controlled-trials.com); the US National Institutes of Health Ongoing Trials Register (www.clinicaltrials.gov); the Australian New Zealand Clinical Trials Registry (www.anzctr.org.au); the World Health Organization International Clinical Trials Registry platform (http://apps.who.int/trialsearch/); and the European Union Clinical Trials Register (https://www.clinicaltrialsregister.eu/). Authors of potentially relevant studies were contacted for further information.

Eligibility

Studies were eligible for inclusion if they were placebo-controlled randomized trials of inhaled or oral corticosteroids in previously well adults (>16 years) with an RTI and acute (<3 weeks) or subacute (3–8 weeks) cough.

Studies were excluded if they had not tested participants for underlying asthma or if participants had an underlying respiratory illness; had recently used corticosteroids, antibiotics or beta-2 agonists; or had an underlying immune-compromising illness. Full details of excluded studies are shown in Table 1.

One reviewer ran the searches and screened titles and abstracts for inclusion. Potentially relevant abstracts were then screened by a second author and included if both were in agreement. The full texts were obtained in the event of uncertainty, and any disagreements were resolved by consensus.
Data extraction and quality assessment

Study quality and risk of bias were assessed independently by two authors, with disagreements resolved by consensus. We assessed methodological quality by examining allocation concealment, randomization; comparability of groups on baseline characteristics, blinding, treatment adherence, attrition bias, and the use of a power calculation, using the tool devised by Higgins et al. \(^\text{22}\) in the Cochrane Handbook. Data were extracted using a predefined extraction template. Study authors were contacted in the event of missing data.

Outcomes

Primary outcomes included the following: (i) severity and duration of cough score and (ii) severity and duration of other symptoms. These were measured using self-reported scoring systems or by any objective measures (e.g. ambulatory cough counts using audio-recording devices and subsequently interpreted using software packages. Secondary outcomes included adverse effects, participant satisfaction with treatment and the subsequent diagnosis of asthma.

Data analysis

Due to substantial heterogeneity and a lack of data, a narrative review of the results was presented. Mean cough scores from each study were detailed, including means of assessment, with associated P values and standard deviation (SD) values if provided. Similarly, data on other symptoms were presented, if available.

Results

Published research

Totally, 2148 citations were identified from the electronic searches. Of these, 32 were selected for further scrutiny. Four trials involving a total of 335 participants met the inclusion criteria (see Fig. 1). Three trials were conducted in Europe (the Netherlands, Germany and Austria)\(^{23–25}\) and one in Thailand.\(^{26}\) Three recruited participants from outpatient medical clinics\(^{24–26}\) and one (the Netherlands)\(^{23}\) from primary care. No study that did not assess participants for asthma prior to recruitment was identified.

Two trials recruited participants with a predominance of acute cough (mean duration of cough before recruitment: 16 and 14.4 days).\(^{24,25}\) One trial recruited mainly those with subacute cough (89 of 133),\(^{25}\) and one recruited those exclusively with subacute cough.\(^{26}\) All trials compared the use of inhaled corticosteroids against that of placebo,\(^{23–26}\) with one permitting complementary use of antibiotics and antihistamines in both groups.\(^{25}\) The type, dose and length of corticosteroid treatment varied, as shown in Table 2.

Cough severity

Three of the four studies assessed the effect of inhaled corticosteroid on cough score (total of 235 participants),\(^{23,24,26}\) of which two showed statistically significant benefits for steroids: fluticasone dipropionate decreased mean cough score from 3.8 to 1.4 (SD: 0.2) versus 3.8–1.9 (SD: 0.1) in the placebo group, \(P = 0.012,^{23}\) and extra-fine hydrofluoroalkane (HFA)–beclomethasone dipropionate versus placebo\(^{24}\) (Table 3). The latter trial reported a statistically significant improvement in the intervention group on an audio measurement of cough frequency \((P = 0.047)\) but no difference between groups with reference to self-reported cough and symptom scores (no \(P\) value provided).\(^{24}\) Two studies\(^{23,24}\) used similar cough symptom diaries, allowing pooling, which showed substantial heterogeneity and a non-significant treatment effect (meta-analysis not shown). Two of the trials\(^{23,24}\) detected benefits used high-dose inhaled corticosteroid (fluticasone dipropionate, 500 \(\mu\)g bd, and beclomethasone dipropionate, 400 \(\mu\)g bd), whereas the

<table>
<thead>
<tr>
<th>Study authors and titles</th>
<th>Reasons for exclusion</th>
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<tbody>
<tr>
<td>Evald T, Munch EP, Kok-Jensen A. Chronic non-asthmatic cough is not affected by inhaled beclomethasone dipropionate. A controlled double blind clinical trial. 1989.</td>
<td>The participants in this study had no preceding respiratory tract infection, hence an unknown cause for cough.</td>
</tr>
<tr>
<td>Han B, Jang SH, Kim YJ et al. The efficacy of inhaled corticosteroid on chronic idiopathic cough. 2009.</td>
<td>The majority of participants had coughs for at least 3 months duration hence falling into the chronic category.</td>
</tr>
<tr>
<td>Ribeiro M, Pereira CA, Nery LE, Beppu OS, Silva CO. High-dose inhaled beclomethasone treatment in patients with chronic cough: a randomized placebo-controlled study. 2007.</td>
<td>The intervention group was given inhaled corticosteroids; however, the control group was given an antitussive drug instead of a placebo.</td>
</tr>
<tr>
<td>Rytila P, Metso T, Heikkinen K et al. Airway inflammation in patients with symptoms suggesting asthma but with normal lung function. 2000.</td>
<td>In addition, a substantial number of participants had a chronic cough prior to recruitment.</td>
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Table 1 Details of excluded studies

Table 2

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trials where no benefit was seen used a medium-level dose (beclomethasone dipropionate, 400 µg daily) and high-level dose (budesonide, 800 µg daily). No data were available regarding effects on cough duration.

Other symptoms
Two studies (235 participants) reported no differences on other symptoms or quality of life.23,25

Smoking
Two trials categorized participants as non-smokers and smokers,23,24 but only one trial investigated for subgroup differences.23 This showed a differential beneficial effect for non-smokers compared with smokers (P < 0.001).

Subsequent asthma diagnoses
No studies reported the subsequent identification of asthma in participants.

Participant satisfaction and adherence to trial medication
No trials reported participant satisfaction data. Two trials reported on estimation of medication compliance,23,24
both by weighing inhalation canisters before and after the trial period.

**Adverse effects**
Out of the 335 participants, one withdrew due to reported intolerance of treatment (no further details provided), one hospital admission occurred due to clinical deterioration (from control group), one participant developed oral thrush (intervention group), three participants developed a hoarse voice (both groups) and one developed a sore throat (control group).

**Quality and risk of bias**
The overall risk of bias for the included studies was graded as unclear. Only one study was considered at low risk of bias.23 Full details are given in Table 4. Most trials did not include a power calculation.

**Ongoing research**
Two ongoing trials looking at oral corticosteroids in persistent cough were identified; no further details were forthcoming from the authors of one study, where recruitment is reported to be complete. The other study has yet to begin recruitment.

**Discussion**

**Summary of results**
We found only four published trials, comprising 335 participants and of mixed quality, and one ongoing trial, investigating the role of inhaled corticosteroids for acute and subacute cough. The published data suggest inhaled corticosteroids may be beneficial for cough severity but not for other associated symptoms, without evidence of significant adverse effects. Non-smokers may be more likely to benefit than smokers. No data were available regarding effects on cough duration and no completed trials of oral steroids were found.

**Strengths and limitations**
This is the first study to systemically search for, and summarize, the randomized, controlled-trial evidence for corticosteroids in acute and subacute cough. Where seen, the beneficial effects were independent of other treatments, such as antibiotics. All trials attempted, using various means, to exclude participants with known and unrecognized asthma and obstructive
<table>
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<tr>
<th>Study</th>
<th>Intervention</th>
<th>Length of treatment</th>
<th>Other treatment permitted</th>
<th>Primary outcome results</th>
<th>Secondary outcome results</th>
<th>Adverse effects</th>
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<tbody>
<tr>
<td>Frank and Dash</td>
<td>Inhaled beclomethasone dipropionate, 100 µg qd</td>
<td>7 days, then assessment. If still symptomatic, continued for further 7 days</td>
<td>Mandatory diphenhydramine and tetracycline</td>
<td>Symptom score per 10 patient days</td>
<td>No difference between groups</td>
<td>One deterioration requiring hospital admission (pyrexia, placebo group)</td>
</tr>
<tr>
<td>Ponsioen et al.</td>
<td>Inhaled fluticasone dipropionate, 500 µg bd (beclomethasone equivalent = 2g daily)</td>
<td>2 weeks</td>
<td>None</td>
<td>Mean cough score (SD)</td>
<td>Reduction in cough score in significant proportion of non-smokers in second week compared with that of smokers ($P = 0.011$).</td>
<td>Intervention group: 1 oropharyngeal candidiasis; 2 hoarseness</td>
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<tr>
<td>Pornsuriyasak et al.</td>
<td>Inhaled budesonide, 400 µg bd (beclomethasone equivalent = 800 µg)</td>
<td>4 weeks</td>
<td>Mucolytics, beta-2 agonists, cough suppressants</td>
<td>Mean cough scores at 2 and 4 weeks: (SD)</td>
<td>Mean changes in cough scores from baseline to 2 weeks and 4 weeks: (SD)</td>
<td>One intolerance to steroid treatment (no further details)</td>
</tr>
<tr>
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<td>Gillissen et al.</td>
<td>Inhaled extra-fine HFA beclomethasone dipropionate, 400 µg bd on Days 1–7 then 200 µg bd on Days 8–11</td>
<td>11 days</td>
<td>None</td>
<td>Reduction in area under the curve (AUC) of cough frequency from 7 a.m. until 11 p.m.: (n = 70) 605.8 in intervention group 847.9 in control group Significant effect favouring treatment (P = 0.047) No SD data available</td>
<td>Mean number of cough epochs from 7 a.m. until 11 p.m.: (n = 70) 28.1 at baseline to 12.7 on Day 11 in intervention 26.4 at baseline to 13.4 on Day 11 in control No P value given No SD data available</td>
<td>None reported</td>
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Table 3 Continued
Corticosteroids for acute and subacute cough

We identified one recently published review in the Cochrane Library by Johnstone et al., assessing the evidence for inhaled corticosteroids in subacute and chronic cough. This review is substantially different from ours in three ways. First, participants were far more likely to have an underlying diagnosis that is not related to an acute RTI by including chronic cough, thereby increasing the heterogeneity of causes of cough. Second, the review omitted studies with participants with acute cough, therefore failing to establish the effect of corticosteroids on an acute respiratory illness. Finally, the authors did not exclude trials looking at participants with cough-variant asthma and eosinophilic bronchitis, both of which are conditions that are known to cause chronic cough and for which inhaled corticosteroids are already a recognized form of treatment. This review found the results to be inconsistent, with substantial heterogeneity between studies, prompting the need, like our review, for further primary research.

**Implications for future research and clinical practice**

Our review suggests that further, adequately powered research is warranted, in primary care, to further clarify the benefits and harms of corticosteroids for adults with acute and subacute cough. Because it is not clear from this review where the dose–response threshold lies, it would appear sensible to test the effects of high-dose (e.g. 40 mg prednisolone daily) oral steroids first. If no effect was seen, it would seem unlikely that even high-dose inhaled steroids would be effective. If benefits were observed, then subsequent trials to test the effects of high- and medium-dose inhaled steroids could be conducted. This evidence is needed before steroids can be recommended for the routine care of adults with acute infective cough, though this review does suggest that high-dose inhaled corticosteroids may be beneficial in some patients with cough secondary to acute LRTI, particularly if they are non-smokers. It would also be important to see, as with beta-2 agonists from previous reviews, if there is a greater benefit in patients who have evidence of airflow obstruction.

**Conclusions**

There is insufficient evidence to recommend the routine use of inhaled corticosteroids for acute infective cough.
in adults at the current time. However, because some trials have shown benefits, it is important to replicate these benefits in further high-quality, adequately powered trials before a firm recommendation of treatment can be made.

Acknowledgements

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Declaration

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Conflict of interest: none.

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