

# Treatments for subacute cough in primary care: a systematic review of randomised clinical trials

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## Abstract

**Background:** Subacute cough following an unspecific viral infection lasting 3 to 8 weeks is common.

**Aim:** To provide a systematic overview of treatment options and outcomes evaluated in randomised clinical trials (RCTs).

**Design and Setting:** Systematic review and meta-analyses

**Method:** We systematically searched PubMed/MEDLINE and the Cochrane Central Register of Controlled Trials (last search March 2017) for RCTs in adult patients with subacute cough. We considered trials evaluating any outcome of any drug or non-drug treatments apart from traditional Chinese and Asian medicines. We combined treatment effects on cough-related outcomes in random-effects meta-analyses.

**Results:** 6 eligible RCTs including 724 patients were identified. They assessed montelukast, salbutamol plus ipratropium-bromide, gelatine, fluticasone propionate, budesonide, nociception-opioid-1-receptor agonist and codeine. 5 studies reported effects on various cough severity scores at various time-points. No treatment option was associated with a clear benefit on cough recovery or other patient-relevant outcomes in any of the studies or in meta-analyses for cough outcomes at 14 and 28 days. Reported adverse events were rather mild and reported for 14% of patients across all treatments.

**Conclusions:** Evidence on treatment options for subacute cough is weak. There is no treatment showing clear patient-relevant benefits in clinical trials.

**Keywords:** cough, subacute, cough score, disease progression, treatment

69 **How this fits in:**

70 Cough after a respiratory infection is one of the most common causes to seek medical  
71 advice. Despite a large number of available treatment options for subacute cough there is no  
72 systematic review evaluating these treatments. We systematically searched for randomised  
73 clinical trials assessing treatment effects and found that the evidence on treatment options  
74 for subacute cough is weak despite the large variety.

75

## Introduction

Cough is one of the most common causes to seek medical advice in primary care (1). Prolonged cough following an upper respiratory tract infection may substantially affect the quality of life and psychosocial well-being (2). Patients may seek medical advice for several reasons, including frustration, irritability, anger, sleep disturbances, and also anxiety of an underlying serious illness such as cancer (3). Treatment strategies for patients with prolonged cough are challenging and also the question whether or not to prescribe antibiotics frequently arises. Antibiotics are not recommended to treat prolonged cough symptoms (4). Even though general practitioners are aware of this, they might feel that their patients urge them to prescribe antibiotics (5). Cough can also have socioeconomically impact due to the consultations and related costs but also due to absence from work and over-the-counter drug prescriptions (6-9). It is estimated that worldwide USD 4 billion are spend on antitussive drugs per year (8). In the United Kingdom the economic burden is estimated to be at least GBP 979 million per year comprising of GBP 875 million in loss of productivity and GBP 104 million to the health care system (9).

In general, cough can be acute (lasting less than 3 weeks), subacute (3 to 8 weeks of symptoms) or chronic (symptoms last for longer than 8 weeks) (10, 11). While chronic cough is most commonly caused by asthma and gastroesophageal reflux disease (GERD) or occurs within an upper airway cough syndrome (12), subacute cough often follows unspecific viral infections causing protracted inflammation of the bronchial mucosa and extensive disruption of epithelial integrity without chronic underlying conditions (4, 13, 14). The American College of Chest Physicians (ACCP) defines subacute cough as cough that “lasts no longer than 8 weeks; the chest radiography findings are negative, ruling out pneumonia; and the cough eventually resolves, usually on its own” (4). Diagnosis is based on medical history and physical examination excluding other underlying causes, such as asthma or GERD (4, 15). Although subacute cough usually improves spontaneously without treatment (10), there is a variety of treatments proposed for alleviation, some of which have been assessed in systematic reviews focusing on very selected drug interventions (16-18). However, there is no systematic review

that evaluates all treatment options. We conducted a systematic review and meta-analysis of randomised clinical trials (RCTs) to provide a wide overview of patient-relevant benefits and harms of available treatments.

## **Methods**

This systematic review is registered in PROSPERO (CRD42017059442).

### Search strategy and inclusion criteria:

An information specialist (HE) searched MEDLINE via PubMed (on 10 February 2017) and the Cochrane Central Register of Controlled Trials (CENTRAL; on 16 March 2017) for RCTs and systematic reviews of RCTs using standard filters (19) without language restrictions (details in Appendix).

We included RCTs in patients aged 16 or older with a cough of 3 to 8 weeks (i.e. subacute) and without known chronic respiratory diseases or other related diagnoses with overlapping symptoms (i.e. GERD, chronic obstructive pulmonary disease [COPD], asthma). We also included trials with slightly shorter or longer cough duration (i.e. a minimum of 2 weeks, a maximum of 10 weeks) or with a less specific definition (i.e. no maximum duration reported, e.g. "longer than 2 weeks") to evaluate further potentially pertinent evidence, given the rather arbitrary cut-off-definition of "subacute". Any reported health outcomes, including any adverse events, were evaluated.

We considered any drug or non-drug treatment, including traditional western cough remedies or medicines, herbal or other natural products and preparations with minimal processing from the European-North-American region (20-22). We did not consider Chinese/Asian herbal medicine (23). A valid and unbiased assessment of such interventions would require a thorough search and evaluation of the Chinese and Asian literature which was beyond the scope of this project. We included studies published in English, German, Italian, Spanish or French. No further eligibility criteria were applied.

We hand-searched reference lists of included trials, pertinent systematic reviews, selected current clinical guidelines of primary care (4, 15) and we screened all citations of pertinent trials using SCOPUS (9 August 2017) to identify potentially relevant RCTs.

Two reviewers independently screened titles and abstracts, conducted the hand-searching and citation screening (AT and BS). Any potentially relevant full text was obtained to determine eligibility. Disagreements were resolved by discussion or with a third reviewer (LGH).

#### Data extraction and risk of bias assessment

From included RCTs, we extracted the year of publication, study period, country, the definition of subacute cough, sample size, type and duration of intervention and control treatment, and duration of follow-up. We extracted any health outcomes and the time-points of their measurement. We sent multiple emails to the corresponding authors of the included studies and asked for additional outcome data (cough scores for 14 and 28 days). However, we obtained no further pertinent data.

All data were independently extracted by two authors (AT and BS). Disagreements were resolved by discussion with a third author (LGH). Two authors independently assessed the risk of bias (BS and LGH) following Cochrane standards (19). Disagreements were resolved by discussion.

#### Statistical analysis

We evaluated all individual study results separately. We also conducted a meta-analysis to assess if treating subacute cough with any treatment is overall more favourable than no treatment. We quantitatively synthesised the effects on cough scores at the same time points using random-effects meta-analyses (we used fixed-effects for sensitivity analyses). We used standardised mean differences (SMD) due to the diversity of cough scores and applied the Hedges'  $g$  (24) method (using the "metacont" function of the "meta"-package (25, 26)). We synthesised only results for cough scores because they were the only reported clinically

comparable outcomes. We investigated the natural disease progression descriptively and by synthesizing cough scores in control groups for the same time-points.

## **Results**

### Results of the search

Our electronic search yielded 691 publications (Figure 1). Six RCTs were eligible (27-32) (Table 1). The studies were typically small, including between 30 and 276 patients (median 96; interquartile range [IQR] 76 to 170), and were conducted between 2000 and 2012 in the United Kingdom (27), Italy (28), Netherlands (31), Thailand (32), Iran (30), or multi-centrally (i.e. Europe, South America and Africa) (29). They explored effects of orally administered montelukast (27), inhaled salbutamol plus ipratropium bromide (28), oral gelatine (30), inhaled fluticasone propionate (31), and inhaled budesonide (32) (Table 1). One study had 3 study arms investigating an orally active selective nociception opioid 1 (NOP1) receptor agonist and oral codeine (29). The comparator was placebo in 5 studies and continued usual care in one. With exception of Zanasi 2014 (28), all studies included some patients with acute or chronic cough (17% to 33%, when stated) but did not report effects for subacute cough (3 to 8 weeks) separately (Table1).

### Risk of bias assessment

Five studies blinded patients and care providers or were reported as “double blind” (27-29, 31). Wang 2015 and Pornsuriyasak 2005 also reported blinded outcome assessment (27, 32). Zanasi 2014 was deemed to have a substantial risk of bias because patients with symptom increase or indications of harm (adverse events) were excluded from analyses (28). Overall, the risk of bias was often unclear due to poor reporting in several studies (Table 2).

### Outcomes

Cough severity score changes between baseline and different time-points were reported for five studies (27-29, 31, 32). They were the primary outcome in Wang 2015 (27), Zanasi 2014

(28), Woodcock 2010 (29), and Ponsioen 2005 (31). In Pornsuriyasak 2005 (32), this was the only outcome with detailed results (Table 1). Wang 2015 used the Leicester Cough Score (as a measure of the cough-specific quality of life). Further endpoints were often intransparently reported and included types of cough-related outcomes, lung function, adverse effects and various other outcomes typically recorded in patient dairies (including sleep affection, absence from work and perception of improvement). No study reported general effects on health-related quality of life (beyond the cough-specific quality of life), hospitalizations, or mortality.

#### Cough severity score

Five studies reported on cough severity scores at various time-points (Table 3) (27-29, 31, 32). No treatment was associated with a clear clinically relevant improvement of cough scores. Two studies reported possible indications for beneficial treatment effects compared to placebo: Ponsioen 2005 reported a favourable effect of inhaled fluticasone over 14 days measured on an unspecified cough score (without any details about validation) ranging on a scale from 0 to 6. They found a statistically significant improvement under fluticasone in the total trial population (including 64% non-smokers) of 0.5 points (95% confidence interval [CI]: 0.1 to 0.9) compared to placebo after two weeks. There was a statistically significant subgroup effect for smoking status (prespecified subgroup), showing an improvement only in non-smoking patients (cough score 0.9 points lower than with placebo; 95%CI: 0.4 to 1.3), but not in smokers (0.1 points; 95% CI: -0.6 to 0.9). This effect was of a similar magnitude as the baseline standard deviation among all patients (1.0 points) and was described as “could be clinically relevant”.(31) However, one third of included patients had acute cough (less than 3 weeks, 23%) or chronic cough (8 to 17 weeks, 10%). There were no separate results for sub-acute cough. The other trial that evaluated inhaled steroids (Pornsuriyasak 2005(32)) found no benefit on cough outcomes at all. Zanasani 2014 reported more favourable effects on cough severity after 10 days of treatment with salbutamol plus ipratropium bromide which did not sustain after 20 days.



The meta-analyses combining effects of the three studies that assessed cough scores 14 days after treatment initiation (Wang 2015, Ponsioen 2005, Pornsuriyasak 2005) and of two studies assessing after 28 days (Wang 2015, Pornsuriyasak 2005) (Figure 2) showed no benefit (14 days: SMD: -0.12; 95% CI: -0.46 to 0.21) and 28 days (28 days SMD: -0.01; 95% CI: -0.24 to 0.21). The sensitivity-analyses using fixed-effect models showed similar results (14 days: SMD: -0.08; 95% CI: -0.27 to 0.11; 28 days: SMD: -0.01; 95% CI: -0.24 to 0.21). Between study heterogeneity was substantial (14 days  $I^2$ : 56%; 95% CI: 0% to 87%) or not meaningful with only two studies (28 days  $I^2$ : 0%) (26).

Overall, cough improved with and without treatment in all studies. In the largest trial (Wang 2015), the improvement under placebo over 14 days and 28 days (score change 3.6; 95% CI: 2.9 to 4.3 and 5.9; 95% CI: 5.1 to 6.7) was above the described minimal clinically important difference of 1.3. The meta-analytically combined improvements of cough at 14 and 28 days were similar or even stronger (Appendix; Figure S1).

#### Other cough-related outcomes

Four studies reported other cough-related outcomes with various levels of details (Table 1) (27, 29-31).

Wang 2015 found no relevant effect of monelukast on overall cough severity, paroxysmal cough severity, the likelihood of cough cessation and cessation of exercise-induced cough and similar rates of patients received further treatments.

Woodcock 2010 found no association of treatment with a NOP1 agonist or with codeine on cough frequency when compared to placebo.

Ponsioen 2005 reported dichotomised success rates (>50% reduction of mean cough scores) of 81% (33 of 41 patients) for non-smokers treated with inhaled fluticasone versus 54% (23 of 43 patients) given placebo. They also observed fewer requests for additional treatment after 14 days of fluticasone compared to placebo (28 of 65 patients; 43% versus 42 of 67 patients; 63%).

The patient's perception of cough improvement was reported in Zolghadrasli 2009 who categorised self-reported response into "no", "poor", "fair", "good", and "excellent" (without further details of operationalization) and described an overall better response with oral gelatine. Ponsioen 2005 made a not further specified statement that after 14 days the treatment was perceived "significantly better" by patients treated with fluticasone.

#### Lung function

Three studies assessed the lung function of patients with overall scarce data (28, 31, 32). Zanasi 2014 reported results for 8 spirometric comparisons of ipratropium plus salbutamol versus placebo over follow-up (showing nominally statistically significant differences in one case for Forced Expiratory Volume in 1 Second [FEV<sub>1</sub>] after 10 days).

Ponsioen 2005 and Pornsuriyasak 2005 stated that there were no statistically significant differences of spirometric parameters (without providing specific outcome data).

#### Adverse events

Five studies reported adverse events (27-31). Across all studies and treatments, adverse events were reported for 98 of 694 analysed patients (14% of patients across all study arms) with absolute rates ranging from 0% to 40% across experimental treatment groups and 0% to 27% across control groups. Adverse events were typically described as rather mild symptoms (mucus production, nasal symptoms, dry mouth, chest or breast discomfort, fainting, headache, nausea, general gastrointestinal complaints; hoarseness, sore throat, oropharyngeal candidiasis). No study reported serious adverse events specifically.

#### Other outcomes

Information on other outcomes was over all studies scarce and intransparently reported. Ponsioen 2005 found no impact of fluticasone on days off work, nocturnal awakenings and lower respiratory tract symptoms but they reported lower sputum scores (not further specified) after 14 days compared to placebo. Woodcock 2010 stated that there was no patient-reported

impact on sleep or daytime activities but a “nonsignificant trend” for higher Stanford sleepiness scores in patients who received NOP1 receptor agonist.

## **Discussion**

### Summary

This systematic review included 6 RCTs assessing the benefits and harms of 7 different treatment regimens for subacute cough. The treatments, settings, outcomes and durations of follow-up were highly heterogeneous. The reporting quality was frequently poor and limited the risk of bias assessment. Overall, there was no clear benefit associated with any of these treatments albeit two studies found some indications for favourable effects.

One trial (Ponsioen 2005 (31)) indicated a beneficial effect of inhaled steroids on cough recovery in the overall study population which was explained by beneficial effects in the subgroup of non-smokers, but this trial included many patients without subacute cough. The other trial with potential indications of benefits (Zanasi 2014 (28)) found a difference with salbutamol plus ipratropium bromide compared to placebo on cough severity scores 10 days after randomisation but not after 20 days. These findings, however, were based on an analysis excluding 10% of patients with “increased cough” or adverse events.

### Strengths and limitations

Various limitations merit closer attention. First, we only searched PubMed/MEDLINE and the Cochrane Central Register of Controlled Trials and might, therefore, have missed trials published in journals which are not indexed in these databases. However, we also screened reference lists, systematic reviews and treatment guidelines without identifying further pertinent studies. Second, although we considered English, German, Italian, Spanish and French literature we excluded 2 articles in Asian languages (i.e. 1 Japanese, 1 South Korean). We also did not consider Chinese/Asian herbal medicine, often assessed in numerous RCTs published in Chinese, South Korean or Japanese (33-37). The inclusion of these treatment

options would have been beyond the scope of this project that aimed to summarise the evidence for treatments which are commonly used by general practitioners and their patients in Europe and North-America. Third, 4 of the 6 included articles had a high risk of bias in at least one domain and the risk of bias was often unclear due to poor reporting. Fourth, with one exception, all RCTs included some patients with shorter or longer cough duration (then defined as acute or chronic cough) and did not report separate treatment effects for patients with a cough duration of 3 to 8 weeks. Hence, the generalisability may be limited. Fifth, we did not assess publication bias due to the limited number of studies (19). Sixth, cough recovery as the most commonly assessed outcome was measured with cough scores that were different across trials (or it was unknown which specific score was used), and the time-points of their measurement was highly heterogeneous between trials. Finally, many other cough-related outcomes were poorly reported, often stating that no significant difference was detected without specifying the effect size.

### Comparison with existing literature

Our results are similar to those of a 2014 Cochrane review of inhaled corticosteroids for acute cough which concluded that “there is no good evidence for or against over-the-counter medicines in acute cough” (38). A 2013 Cochrane review and a systematic review by El-Gohary and colleagues evaluated inhaled corticosteroids for subacute and chronic cough (16) as well as for acute and subacute cough (17). Both reviews identified the same two studies (31, 32) for subacute cough that we found and the articles similarly conclude that “the data were too mixed to be able to draw any conclusions.”(16) and that there is “insufficient evidence to recommend the routine use of inhaled corticosteroids [...]” (17). Remarkably, antitussive agents that are currently used in clinical practice were developed several decades ago and there has been little progress in the meantime although the need of effective antitussive treatments seems obvious.(8) Our systematic review identified no RCTs for other potential treatment options, such as oral corticosteroids, which are efficient against asthma and COPD where the cough is also mediated by inflammatory processes as in subacute cough (39-41).

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328 Implications for research and practice

329 Overall, our systematic review clearly emphasises the limited available evidence on  
330 therapeutic options for subacute cough. However, it also shows that the symptoms diminish  
331 over time as natural course of the self-limiting disease. Therefore, considering the problem of  
332 overtreatment (42, 43), spending time with the patient and explaining the illness might be  
333 crucial for patient satisfaction (44). Our review indicates that despite being one of the most  
334 common causes to seek medical advice in primary care, there is no beneficial treatment for  
335 subacute cough.

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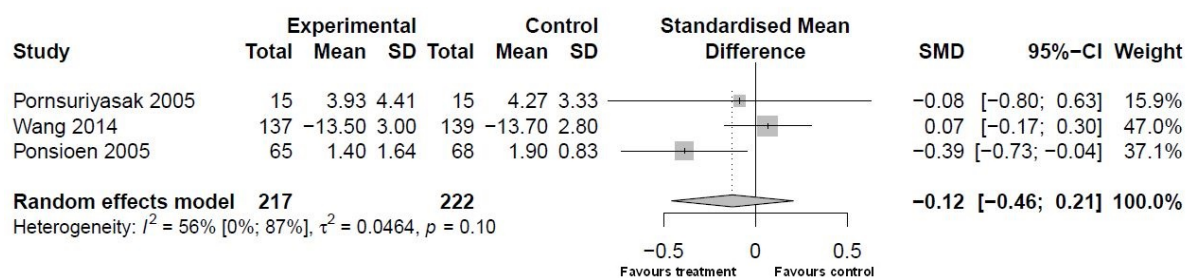
443 **Figure 1:** Study selection



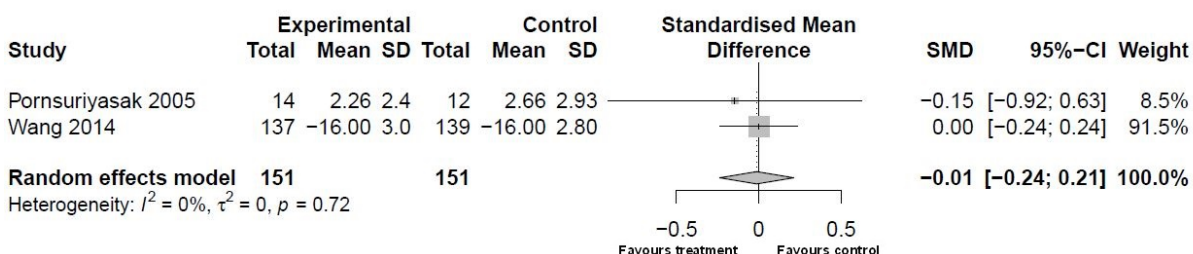
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**Figure 2: Treatment effects on cough scores after 14 days (A) and 28 days (B)**

**A.**



**B.**



The score used in Wang 2014 has a different direction i.e. scores > 0 meant better cough score while in the other studies it was the other way. Therefore, to unify the direction of the scores we multiplied the mean of Wang 2014 with -1.

**Table 1:** Characteristics of randomised clinical trials assessing different treatment for subacute cough.

Publication	Year conducted	Country	Number of patients	Cough duration	Number of patients with subacute cough	Intervention(s) and control	Duration of treatment Duration of follow-up	Primary outcome and time-point of measurement	Other outcomes
Wang 2014(27)*	2011-2012	United Kingdom	276	2-8 weeks	Not reported <sup>a</sup>	Montelukast 10 mg daily vs. placebo	14 days <sup>b</sup> 28 days	Leicester cough score questionnaire (cough specific quality of life) at day 14 and 28	<ul style="list-style-type: none"> <li>• Overall cough severity</li> <li>• Paroxysms of cough</li> <li>• Cough cessation</li> <li>• Cessation of exercise induced cough</li> <li>• Further interventions for cough</li> <li>• Adverse events</li> </ul>
Zanasi 2014(28)	2011-2012	Italy	92	≥3 weeks and <4 weeks after URTI	92 (100%)	Salbutamol 1.875 mg/0.5 mL plus ipratropium bromide 0.375 mg/0.5 mL vs. placebo	10 days 20 days	Cough severity (daytime and night-time separately) at day 10 or 20 <sup>c</sup>	<ul style="list-style-type: none"> <li>• Lung function</li> <li>• Adverse events</li> </ul>
Woodcock 2010(29)	NR	United Kingdom, Latin America, South Africa	91	≥2 weeks and ≤90 days after viral URTI	Not reported <sup>d</sup>	NOP1 receptor agonist 100mg twice daily vs. codeine 30mg twice daily vs. placebo	5 days 5 days	Cough severity at day 5	<ul style="list-style-type: none"> <li>• Cough frequency</li> <li>• Stanford sleepiness scores</li> <li>• Patient dairy<sup>e</sup></li> <li>• Adverse events</li> </ul>
Zolghadrasli 2009(30)	2006-2007	Iran	100	>3 weeks	83 (83%) <sup>f</sup>	Gelatine 5cc (a teaspoon) 3 times a day vs. continuation of the previous antitussive medication	3-5 days 6-10 days	Not reported	<ul style="list-style-type: none"> <li>• “Subjective assessment of improvement”</li> <li>• Adverse events</li> </ul>
Ponsioen 2005(31)*	2000-2001	Netherlands	133 (89 subacute cough 3-8 weeks)	≥ 2 weeks <sup>g</sup>	89 (67%) <sup>g</sup>	500 µg inhaled fluticasone propionate, twice daily vs. placebo	14 days 14 days	Cough score (daytime) at 14 days	<ul style="list-style-type: none"> <li>• Cough score improvement &gt;50%</li> <li>• Perception of improvement</li> <li>• Additional treatment required after 14 days</li> <li>• Days off work</li> <li>• Lung function</li> <li>• Patient dairy<sup>h</sup></li> <li>• Adverse events</li> </ul>
Pornsuriyasak 2005(32)*	NR	Thailand	30	>3 weeks	Not reported <sup>i</sup>	Four puffs of 100 µg budesonide, twice daily vs. placebo	28 days 28 days	Not reported	<ul style="list-style-type: none"> <li>• Symptom score (at 14 and 28 days)</li> <li>• Lung function</li> </ul>

<sup>a</sup>Mean duration 5 weeks (SD 1.9) in the intervention and 4.8 weeks (SD 1.8) in the control group with 48% of patients ≤4 weeks. No subgroup for subacute cough (3 to 8 weeks) reported.

<sup>b</sup>Participants could choose to continue treatment

<sup>c</sup>Reporting not clear

<sup>d</sup>Persistent cough described as “subacute cough” after a viral upper respiratory tract infection lasting 14 to 90 days. Median cough duration of 33 days; range: 16 to 99 days. No subgroup for subacute cough (3 to 8 weeks) reported.

<sup>e</sup>Including cough frequency, lack of sleep, interference with daytime activity and a general question on “how the cough has affected” the patient. No results are reported beyond stating that there were “no significant differences”.

<sup>f</sup>Included 17 of 100 patients (17%) with cough lasting more than 8 weeks. No subgroup for subacute cough (3 to 8 weeks) reported.

<sup>g</sup>Included 31 of 133 patients (23%) with cough lasting 2 to 3 weeks and 13 patients (10%) with cough lasting more than 8 weeks. No subgroup for subacute cough (3 to 8 weeks) reported.

<sup>h</sup>Including cough, sputum production, wheezing, shortness of breath, chest tightness, number of awakenings, number of cigarettes smoked

<sup>i</sup>Included patients with cough lasting longer than 3 weeks and only presents the mean cough duration at baseline (treatment group: 5.93 weeks, SD 1.94; control group: 4.66 weeks, SD 2.05). No subgroup for subacute cough (3 to 8 weeks) reported.

\*Included in meta-analysis

Abbreviations: URTI= upper respiratory tract infection; LCQ=Leicester Cough Questionnaire; VCD=Verbal Category Descriptive

**Table 2:** Risk of bias summary of the included studies

	Random sequence generation	Allocation concealment	Blinding of patients and personnel	Blinding of outcome assessment	Analysed as randomised	Attrition bias and missing data (>10%)
Wang 2014(27)	+	+	+	+	+	- <sup>a</sup>
Zanasi 2014(28)	+	?	+ <sup>b</sup>	? <sup>b</sup>	+	- <sup>c</sup>
Woodcock 2010(29)	?	?	+ <sup>b</sup>	? <sup>b</sup>	+	(+) <sup>d</sup>
Zolghadrasli 2009(30)	?	?	-	-	?	+
Ponsioen 2005(31)	+	+	+ <sup>b</sup>	? <sup>b</sup>	+	+
Pornsuriyasak 2005(32)	?	?	+	+	?	(-) <sup>e</sup>

<sup>a</sup> Less than 80% of patients with outcome data at week 4 ("co-primary" outcome). For 2 weeks ("co-primary" outcome), 87% of patients with primary outcome data.

<sup>b</sup> Study placebo-controlled and reported as "double-blind". We think it is likely that patients and personnel conducting the intervention were blinded but this is unclear for the outcome assessor and the outcomes are subjective.

<sup>c</sup> Of 92 randomised patients, 9 were excluded from the analysis due to adverse events (n=5) or "increased cough" (n=4).

<sup>d</sup> For the primary outcome (cough severity scores), only 2 of 91 randomised patients dropped out. In 17 out of 91 patients there were technical problems with the device used for objectively monitoring cough (secondary outcomes).

<sup>e</sup> For the 2-week cough score results, data for all 30 randomised patients were available. For the 4-week time-point, 3 of 15 randomised patients in the control group (20%) had no data assessment (1 of 15 in the experimental treatment group; 7.5%).

**Table 3:** Five randomised controlled trials reporting cough severity scores at different time-points

Publication	Treatment comparison	Time-point (days)	Patients analysed/ randomised	Outcome Definition	Experimental Mean (95% CI)	Control Mean (95% CI)	Group Difference Mean (95% CI)
Wang 2014(27)	Montelukast vs placebo	14	Exp: 137 <sup>a</sup> /137 Ctrl: 139 <sup>a</sup> /139	Change in the Leicester Cough Questionnaire between baseline and two follow-up stages	2.7 (2.2 to 3.3) <sup>b</sup>	3.6 (2.9 to 4.3) <sup>b</sup>	-0.9 (-1.7 to -0.04) <sup>c,d</sup>
		28	Exp: 137 <sup>a</sup> /137 Ctrl: 139 <sup>a</sup> /139		5.2 (4.5 to 5.9) <sup>b</sup>	5.9 (5.1 to 6.7) <sup>b</sup>	-0.5 (-1.5 to 0.6) <sup>c,d</sup>
Zanasi 2014(28)	Salbutamol plus ipratropium bromide vs. placebo	10	Exp: 41/46 Ctrl: 42/46	The change in both daytime and nighttime cough severity, as assessed by the verbal category descriptive score	Daytime: 1.32 (0.93 to 1.71) <sup>e</sup> Nighttime: 0.37 (0.17 to 0.57) <sup>e</sup>	Daytime: 2.14 (1.73 to 2.55) <sup>e</sup> Nighttime: 0.74 (0.49 to 0.99) <sup>e</sup>	NR
		20	Exp: 41/46 Ctrl: 42/46		Daytime: 0.41 (0.17 to 0.65) <sup>e</sup> Nighttime: 0.15 (0.02 to 0.28) <sup>e</sup>	Daytime: 0.64 (0.38 to 0.90) <sup>e</sup> Nighttime: 0.17 (0.04 to 0.30) <sup>e</sup>	NR
Woodcock 2010 A(29)	NOP1 receptor agonist vs placebo	5	Exp: 26/27 Ctrl: 30/30	Change in cough severity scores	-0.57 (NR)	-0.49 (NR)	NR
Woodcock 2010 B(29)	Codeine vs placebo	5	Exp: 33/34 Ctrl: 30/30		-0.72 (NR)	-0.49 (NR)	NR
Ponsioen 2005(31)	Fluticasone propionate vs. placebo	14	Exp: 65/67 Ctrl: 68/68	Cough score	1.4 (0.2 SEM)	1.9 (0.1 SEM)	NR
Pornsuriyasak 2005(32)	Budesonide vs. placebo	14	Exp: 15/15 Ctrl: 15/15	Symptom score	3.93 (1.70 to 6.16) <sup>e</sup>	4.27 (2.58 to 5.96) <sup>e</sup>	NR
		28	Exp: 14/15 Ctrl: 12/15		2.26 (1.00 to 3.52) <sup>e</sup>	2.66 (1.00 to 4.32) <sup>e</sup>	NR

<sup>a</sup>Missing data imputed by study authors using last observation carried forward: 14 days: 19 (Exp) and 17 (Ctrl); 28 days: 26 (Exp) and 29 (Ctrl).

<sup>b</sup>Mean difference in scores compared to baseline.

<sup>c</sup>Adjusted for numerous baseline variables (baseline scores, age, sex, duration of cough, pertussis status, pertussis immunisation status, atopy, paroxysmal cough severity, and exercise-induced cough severity); unadjusted analysis slightly and not relevantly different. Higher LCQ score indicates higher quality of life. Therefore the result is in favour of the control.

<sup>d</sup>Higher Leicester Cough Questionnaire score indicates higher quality of life, i.e. the result is in favour of the control. For all other cough scores, lower values indicate fewer cough symptoms.

<sup>e</sup>95% CI calculated by us from standard deviation.

Abbreviations: CI=Confidence Interval; Exp=Experimental group; Ctrl=Control group; NR=Not reported; SEM=Standard error of mean

