Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease (Review)

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[Intervention Review]

Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease

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ABSTRACT

Background

Individuals with chronic bronchitis or chronic obstructive pulmonary disease (COPD) may suffer recurrent exacerbations with an increase in volume or purulence of sputum, or both. Because of the personal and healthcare costs associated with exacerbations, any therapy that reduces the number of exacerbations is useful. There is a marked difference among countries in terms of prescribing of mucolytics depending on whether or not they are perceived to be effective.

Objectives

Primary objective: to determine if treatment with mucolytics reduces the frequency of exacerbations, days of disability, or both, in participants with chronic bronchitis or chronic obstructive pulmonary disease, or both.

Secondary objectives: to determine if mucolytics lead to an improvement in lung function or quality of life and to determine the frequency of adverse effects associated with mucolytics.

Search methods

We searched the Cochrane Airways Group Specialised Register and reference lists of articles on ten separate occasions, the most recent being in July 2012.

Selection criteria

We included randomised studies that compared oral mucolytic therapy with placebo for at least two months in adults with chronic bronchitis or COPD. We excluded studies of people with asthma and cystic fibrosis.

Data collection and analysis

The review analysed summary data only, the majority from published studies. For earlier versions, one author extracted data, which was rechecked in subsequent updates. In later versions, we double-checked data extraction. We then entered data into RevMan for analysis.

Main results

Two further trials have been added to the review for the 2012 update. There are now 30 trials in the review, recruiting a total of 7436 participants. Allocation concealment was not clearly described in the early trials, and selection bias may have inflated the results, which reduces our confidence in the findings of these trials.

The likelihood of being exacerbation-free during the study period (22 trials in 4886 participants with a mean duration of 10 months) was greater in the mucolytic group for the double-blind trials (Peto odds ratio (OR) 1.84; 95% confidence interval (CI) 1.63 to 2.07). However, the more recent trials show less benefit of treatment than the earlier trials included in this review. The overall number needed to treat with mucolytics to keep an additional participant free from exacerbations over 10 months was seven (NNTB 7; 95% CI 6 to 9). The use of mucolytics was associated with a reduction of 0.04 exacerbations per participant per month (95% CI -0.04 to -0.03) compared with placebo; that is about 0.48 per year, or one exacerbation every two years. There was very high heterogeneity in this outcome (I^2 = 87%) so results need to be interpreted with caution.

The number of days of disability per month also fell (mean difference (MD) -0.48; 95% CI -0.65 to -0.30) in 12 trials on 2305 participants. There was no clinically important improvement in lung function or consistent impact on quality of life with mucolytics. Mucolytic treatment was not associated with any significant increase in adverse effects, including mortality (Peto OR 0.75; 95% CI 0.35 to 1.64) in six trials on 1821 participants.

Authors' conclusions

In participants with chronic bronchitis or COPD, treatment with a mucolytic may produce a small reduction in acute exacerbations, but may have little or no effect on the overall quality of life. The effects on exacerbations shown in early trials were larger than those found in the more recent studies. This may be because the earlier smaller trials were at higher risk of selection or publication bias, so the benefits of treatment may not be as large as suggested by the previous evidence.

PLAIN LANGUAGE SUMMARY

Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease

Mucolytics are a group of medications used in the treatment of people with chronic obstructive pulmonary disease (COPD) or chronic bronchitis. This review assessed how effective they were in these patients. Mucolytic medications are intended to break up or loosen sputum (or both) and make it easier to cough up. The review authors looked at 30 studies with a total of 7436 patients. The results showed that if the medication was taken on a regular basis there could be a small reduction in the number of exacerbations (worsening of disease/symptoms) experienced by the patient. The number was approximately one less patient exacerbating for every seven treated with a mucolytic over 10 months. However, the studies included in the review were a mix of small older ones and large newer ones with the newer ones not showing as much benefit. This fact reduces our confidence in the results found. The medicines appear to be safe and well-tolerated but they do not slow the worsening of lung function in people with COPD.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Mucolytic versus placebo for chronic bronchitis or chronic obstructive pulmonary disease

Patient or population: patients with chronic bronchitis or chronic obstructive pulmonary disease
Settings: community
Intervention: mucolytic versus placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Mucolytic versus placebo				
Patients with no exacerbations in study period Follow-up: 2 to 36 months	**415 per 1000**	**572 per 1000** (544 to 600)	**OR 1.88** (1.68 to 2.11)	5149 (24 studies)	⊕⊕◯◯ **low**[1,2,3]	
Adverse effects Follow-up: 2 to 36 months	**205 per 1000**	**177 per 1000** (151 to 207)	**OR 0.83** (0.69 to 1.01)	5176 (18 studies)	⊕⊕⊕◯ **moderate** [1,4]	
Death during study period Follow-up: 2 to 36 months	**16 per 1000**	**12 per 1000** (6 to 27)	**OR 0.75** (0.35 to 1.64)	1821 (6 studies)	⊕◯◯◯ **very low**[1,5,6]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **OR:** odds ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

[1] (-1 limitations) Most trials at risk of selection bias (see Figure 5).
[2] (-1 inconsistency) Inconsistent results between trials and more recent trials show smaller treatment effects.
[3] Funnel plot shows no small studies with negative effects.
[4] Data from some of the larger studies could not be included in this analysis because event rates exceeded the number of participants.
[5] (-2 imprecision) Results include the possibility of a large difference in either direction.
[6] Very few studies contribute data to this outcome.

BACKGROUND

Description of the condition

At least 50% of smokers will develop chronic bronchitis (Redline 1991). This is often defined as the presence of chronic productive cough for three months in each of two successive years in a patient in whom other causes of chronic cough such as tuberculosis, carcinoma of the lung and heart failure have been excluded (MRC 1965). Many patients with chronic bronchitis also have chronic obstructive pulmonary disease (COPD). In the latest global COPD guidelines (GOLD 2011), COPD is defined as a common, preventable and treatable disease, characterised by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and co-morbidities contribute to the overall severity in individual patients.

It is estimated that COPD is the fourth or fifth most common single cause of death worldwide. There is currently no cure for COPD, although it is both a preventable and treatable disease. Apart from smoking cessation and long-term oxygen therapy in hypoxic patients, no intervention has been shown to reduce mortality (GOLD 2011).

People with COPD may experience chronic and progressive breathlessness, cough and sputum production, which in turn may lead to restricted activity and worsening quality of life. Exacerbations occur with increasing frequency as the disease becomes more severe. They are characterised by an increase in breathlessness, plus greater volume or purulence of sputum, or both. Exacerbations accelerate decline in lung function and are associated with worse quality of life and higher mortality. They also increase healthcare costs (GOLD 2011). Thus, treatments that reduce the frequency and duration of acute exacerbations are likely to have benefits in COPD management.

How the intervention might work

Mucolytics are agents which are believed to increase the expectoration of sputum by reducing its viscosity. Examples of mucolytics include N-acetylcysteine, iodinated glycerol and ambroxol. Given that oxidative stress is thought to be an amplifying mechanism in COPD (Rahman 2005), another property of mucolytics such as N-acetylcysteine that may be useful in chronic airways disease is their antioxidant effect.

Why it is important to do this review

In some European countries mucolytics are widely prescribed in the belief that they reduce the frequency of exacerbations or reduce symptoms or both in patients with chronic bronchitis. In contrast, in other parts of the world, such as the UK and Australasia, mucolytics are used infrequently because they are perceived to be ineffective. As there are theoretical reasons why mucolytics may work in both chronic bronchitis and COPD, and treatments are needed that reduce exacerbations to reduce morbidity and costs, this review will help determine the true effect of this class of medicines.

OBJECTIVES

Primary objective

To determine whether or not treatment with mucolytics reduces the frequency of exacerbations or days of disability (or both) in participants with chronic bronchitis or COPD.

Secondary objectives

To determine whether or not mucolytic treatment leads to an improvement in lung function or quality of life; further to determine the frequency of adverse effects associated with mucolytic treatment.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised, placebo-controlled studies of oral mucolytics administered regularly for a period of at least two months.

Types of participants

We included adults (over 20 years of age) with chronic bronchitis as defined by the British Medical Research Council (cough and sputum on most days during at least three consecutive months for more than two successive years) or COPD as defined by the criteria of the American Thoracic Society, GOLD (GOLD 2005), European Respiratory Society or the World Health Organization (WHO). Studies on patients with asthma or cystic fibrosis were excluded.

Types of interventions

Participants received regular treatment with oral mucolytics compared with placebo for at least two months. Oral mucolytics included the following compounds: N-acetylcysteine (NAC), S-carboxymethylcysteine, bromhexine, ambroxol, erdosteine, sobrerol, cithiolone, letosteine and iodinated glycerol. Two studies of newer agents were included in the 1999 update of this review. These were Ekberg-Jansson 1999 in which a thiol donor derivative of NAC with antioxidant properties, N-isobutyrylcysteine, was used; and Meister 1999, which used a mucus modifying agent, myrtol. In 2012, we included a study of cineole (Worth 2009).

We excluded studies of inhaled mucolytics and combinations of mucolytics with antibiotics and mucolytics with bronchodilators as well as studies of deoxyribonuclease or proteases such as trypsin.

Types of outcome measures

Primary outcomes

1. Exacerbations, as measured by the number of patients with no exacerbations in the study period, as well as the total number of acute exacerbations per participant. Exacerbations were defined as an increase in cough and by the volume and/or purulence of sputum.
2. Number of days of disability variously defined as days in bed, days off work or days where the patient was unable to undertake normal activities. We also assessed days on antibiotics.

Secondary outcomes

1. Measures of lung function, including forced expiratory volume in one second (FEV_1), forced vital capacity (FVC) and peak expiratory flow rate (PEFR)
2. Adverse effects of treatment
3. Hospitalisation and mortality
4. Quality of life

We had intended to use symptom scores as a secondary outcome measure but it became clear that symptoms were not reported in a consistent fashion and it was not possible to standardise the symptom scores. As more studies use validated quality of life scores, we have added these as an analysis.

Adverse events were not usually reported in detail and were usually mild and self limiting, so we have only entered the total number of adverse events.

Search methods for identification of studies

Electronic searches

We identified studies using the Cochrane Airways Group Specialised Register of trials, which is derived from systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and CINAHL, and handsearching of respiratory journals and meeting abstracts (see Appendix 1 for more details). For the 1996 and 1999 reviews, were searched all records in the Specialised Register coded as 'COPD' using the following terms:

mucolytics or N-acetylcysteine or bromhexine or S-carboxymethylcysteine or ambroxol or sobrerol or iodinated glycerol

In 2002, we widened the search to:

(mucolytic* or "mucociliary clearance" or mucoactive or N-acetylcysteine or bromhexine or S-carboxymethylcysteine or ambroxol or sobrerol or "iodinated glycerol" or N isobutyrylcysteine or myrtol or NAC or methylcysteine or carbocysteine or erdosteine or strepronin* or gelsolin or MESNA)

In May 2011, we ran a search using the above terms from 2008 to the present date. We repeated the search in July 2012 to bring the review up to date prior to publication.

We conducted a further search adding the term 'cineole' for all years, as randomised controlled trials using this compound have been reported.

Searching other resources

We checked the references of all the papers and reviews for which we obtained the full text for any other relevant articles. We asked other researchers in the field to provide any other references, and remain open to unsolicited suggestions as to potentially eligible studies.

Data collection and analysis

Selection of studies

At least one review author (PB and PP for original review, PP and Jimmy Chong (JC) for updates) assessed all the abstracts obtained from the search of the Cochrane Airways Group Register. We obtained the full text for those which appeared to fit the criteria for inclusion (or if this was not clear from the abstract). Two review authors (PB and PP) independently selected trials for inclusion in the review for the original review. Disagreement over inclusion was resolved by discussion between the two review authors. Six translators (two of whom were medically trained) assessed papers published in languages other than English. For this update, the lead review author (PP) was assisted by another Cochrane review author (JC) in determining study eligibility and data to be extracted.

Data extraction and management

For the earlier versions, if there were insufficient data in the paper, we requested further information by writing to the author or to the pharmaceutical company sponsoring the study. We abstracted data onto worksheets before entering them into the Review Manager

software (RevMan 2011). We double-checked all entries against the original paper. In the 1999 update we rechecked all the original data.

Assessment of risk of bias in included studies

We used the following assessment for concealment of allocation.

1. Low risk of bias: if there was true randomisation, i.e. a central randomisation scheme with randomisation by external person or use of coded containers/envelopes.
2. Unclear: insufficient information was available.
3. High risk of bias: if there was alternate allocation, reference to case record number, date of birth, day of the week, or an open test or random number.

Measures of treatment effect

We analysed continuous data using the mean difference (MD) (except for the outcomes 'exacerbation rate regardless of study duration' and 'FEV_1,% change in FEV_1 or PEFR' for which we used standardised mean differences (SMD)). We used the Peto odds ratio for dichotomous data and reported the results with 95% confidence intervals (CI).

Unit of analysis issues

We calculated exacerbation rates and days of disability by dividing the number of events by the number of participants and the number of months of the study (i.e. per patient per month). We also scaled the standard deviation for monthly rates in the same way.

Data synthesis

We used summary statistics rather than individual patient data. We used a fixed-effect model.

For the outcome of having 'no exacerbation in the study period', we calculated a number needed to treat (to benefit) (NNTB) based upon the pooled Peto odds ratio (Cates 2002), with baseline risk taken from the pooled control group event rate (total number of events divided by the overall number of participants in the placebo group multiplied by 100).

Subgroup analysis and investigation of heterogeneity

We planned a priori subgroup analyses on type of mucolytic, dose, duration, country of study, disease severity and whether or not participants were included as they had a history of exacerbations. Following the publication of the BRONCUS study (Decramer 2005), which suggested a differential effect of mucolytics depending on concomitant treatment, we included an analysis by whether or not concomitant inhaled corticosteroids were permitted.

For the 2012 update we have carried out a post hoc investigation of time trends in the data on participants with one or more exacerbations by comparing the results of trials published since 2000 to those published earlier.

Sensitivity analysis

For the 2012 update we have explored the heterogeneity in the results on exacerbations, and have looked at sensitivity analysis using data from trials assessed as being at a low risk of selection bias (on the basis of allocation concealment).

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

For details of search history see Table 1. There have now been more than 764 abstracts identified from the iterative computer searches. After excluding studies that were clearly ineligible, we have reviewed full texts for 98 papers.

We performed two searches in 2008; these yielded two further studies (Bachh 2007; Zheng 2008) and another report (Moretti 2007) of an earlier study (Moretti 2004).

For the 2012 update, we identified 72 potentially eligible abstracts and papers from the search. Several were further reports of the PEACE study (Zheng 2008) or the EQUALIFE study (Moretti 2004) already included in this review (e.g. Ballabio 2008). We reviewed seven full texts: two related to the same study of cineole in COPD (Worth 2009; Worth 2010) that proved eligible. Also eligible was the COOPT study comparing NAC, inhaled corticosteroids or placebo in primary care patients with COPD or chronic bronchitis (Schermer 2009). Among the ineligible studies was a study of cineole in COPD (Wilhelmi 2010) that contained no useable data on the primary outcome of exacerbations. We found a potentially eligible abstract (Moretti 2011) and added it to Studies awaiting classification. We excluded another study (Lukas 2005) of NAC in chronic bronchitis as there were no data on the outcomes of interest in this review.

Additionally, the Cochrane Airways Group was informed about a study of neltenexine (Cattaneo 2001), another mucolytic. This study had been excluded in an earlier version, and remains so, as the study ran only for 20 days. Ekberg-Jansson 1999 was identified by the review authors in the course of reading the *European Respiratory Journal*.

There are three reports of the PEACE study (Tatsumi 2007a; Tatsumi 2007b; Zheng 2008). The main randomised controlled trial (RCT) of Zheng 2008 was conducted in 22 centres in China; the other two reports are of a study on a separate group of 142 patients in Japan conducted as an 'open label' study. This difference has been confirmed by the primary authors. At this stage, the Tatsumi study is excluded from this review because of the open label design.

In one unpublished study, we obtained data from the abstract and from further information provided by the pharmaceutical company (Nowak 1999).

We wrote to the authors of 10 studies (Allegra 1996; Babolini 1980; Boman 1983; Castiglioni 1986; Christensen 1971; Jackson 1984; Grillage 1985; Nowak 1999; Parr 1987; Petty 1990) requesting more information. We received further data for two studies (Allegra 1996; Nowak 1999). Dr Petty responded to our letter but could not supply the data because they were held by a pharmaceutical company (the company has not replied despite two letters). Dr Boman also wrote to say that he was unable to supply us with more data. This was also the case for Novartis Pharmaceuticals (UK) who responded on behalf of two authors (Jackson 1984; Parr 1987) and Parke Davis Research Laboratories (Grillage 1985). We received no reply to our request for further data relating to the remaining three studies (Babolini 1980; Castiglioni 1986; Christensen 1971) despite two letters. We also wrote to the authors of Olivieri 1987 to clarify the error measurement used, but received no reply. Pharmaceutical companies notified us of two studies (Meister 1986; Meister 1999), the former was unpublished. They also provided further information on four studies (Meister 1986; Meister 1999; Nowak 1999; Pela 1999). In 2008 we contacted an author of the COOPT study 'A double-blind placebo-controlled trial comparing the efficacy and cost-effectiveness of inhaled fluticasone propionate versus oral n-acetylcysteine in the treatment of patients with COPD in general practice' (Clinical Trials identifier: NCT00184977) conducted from 1998 to 2003 to ascertain whether any data might be made available for this review. This study has now been published and is included in the review (Schermer 2009). In 2012 we contacted the lead author of Decramer 2005 to clarify conflicting information on quality of life in the published report and the lead author helpfully provided us with information on the St George's Respiratory Questionnaire (SGRQ).

Included studies

There are now 30 RCTs included in the review, recruiting a total of 7436 participants. Full details of each study are described in Characteristics of included studies.

There are eight studies (Bachh 2007; Decramer 2005; Malerba 2004; Moretti 2004; Nowak 1999; Pela 1999; Worth 2009; Zheng 2008) of mucolytics in COPD. A recent study in primary care included both chronic bronchitis and those with COPD (Schermer 2009).

All but two studies were randomised, double-blind and placebo-controlled with a parallel-group design. Study duration ranged from 2 to 36 months, averaging 10 months. Ten studies had a run-in period (Allegra 1996; Boman 1983; Ekberg-Jansson 1999; Malerba 2004; McGavin 1985; Meister 1999; Moretti 2004; Olivieri 1987; Schermer 2009; Zheng 2008). Two studies were described as randomised and placebo-controlled but not double-blind. One was labelled as 'open' (Pela 1999) and the second (Bachh 2007) was a 'single-blind' trial. Because of the potential for bias, these are reported separately in the analyses of the primary outcomes.

In one study in primary care practices (Schermer 2009), NAC 600 mg daily was compared with placebo as well as inhaled fluticasone 500 mcg BD (twice daily) in a three-arm, double-dummy design study. This review used data from the NAC and the placebo arms only.

Inclusion and exclusion criteria

All studies stated which criteria the participants fulfilled criteria for chronic bronchitis or COPD (except Nowak 1999, which has been published in abstract form only). Exclusion criteria varied and some studies did not report if patients with other respiratory illness were excluded.

Lung function

All but two studies (Grassi 1976; Parr 1987) reported baseline lung function using PEFR, FEV_1 or FEV1% predicted. Where studies reported pre- and post-bronchodilator lung function we have used the latter.

Age of participants

The mean age of participants ranged from 40 to 67 years. Most studies had an upper age limit for participants.

Sex of participants

All but three of the studies reported the numbers of males in the study and this ranged from 44% to 85%. In one study "almost all" of the participants were reported as being male.

Smokers

All but five studies reported the percentage of current or ex-smokers, and this ranged from 55% to 100%.

Mucolytics

In 15 of the studies the mucolytic was N-acetylcysteine (NAC). Other study treatments were carbocysteine (N = 4), ambroxol (N = 3), sobrerol, letosteine, cithiolone, iodinated glycerol, N-isobutyrylcysteine (NIC), myrtol, erdosteine and cineole.

Countries

Twelve studies were conducted only in Italy, three in Scandinavia, four in the United Kingdom, four in Germany, three in several European countries, one in The Netherlands, and one each in the United States, China and India.

Excluded studies

See the Characteristics of excluded studies for the reasons for exclusion.

Risk of bias in included studies

Twenty-eight randomised controlled trials had a Jadad quality score of at least 2 out of 5, and 22 had a score of 3 or more. The two non double-blind studies had Jadad scores of 0 and 1.

Allocation

Potential for bias in most studies was regarded as unclear, in that the authors stated that the study was randomised, but not how this was achieved, where it was done, or how it was concealed. The recent BRONCUS (Decramer 2005), PEACE (Zheng 2008) and COOPT studies (Schermer 2009) were graded as low risk, as the method of concealment of randomisation was carefully outlined and appropriate. In two studies (Boman 1983; Castiglioni 1986) the concealment was regarded as high risk, as they used tables of random numbers independently at each study centre. Most studies reported the baseline characteristics of treatment groups, which were well-matched at baseline.

Blinding

Most studies reported that the placebo was identical in appearance to the active treatment. Pela 1999 was an open study and was classified as high risk, as was Bachh 2007.

Incomplete outcome data

The number of dropouts ranged from 0% (Bachh 2007; Bontognali 1991; Cremonini 1986) to 37% in the three-year BRONCUS study (Decramer 2005) and 43% in another three-year study conducted in a general practice setting (Schermer 2009). In most of the older studies, the analyses were performed on the participants who completed the study (per protocol), whereas in more recent studies, analyses tended to be performed on an intention-to-treat basis.

Effects of interventions

See: **Summary of findings for the main comparison** Mucolytic versus placebo for chronic bronchitis or chronic obstructive pulmonary disease

Patients with no exacerbations in study period

We added this dichotomous comparison for the 1999 update and refined it for the 2012 update. The odds ratio (OR) for having no exacerbation over the entire study period for treatment with mucolytics in double-blind trials was increased compared with placebo (Peto OR 1.84; 95% confidence interval (CI) 1.63 to 2.07; Figure 1; Analysis 1.1). This gives a number needed to treat to benefit (NNTB) of 7 (95% CI 6 to 9; Figure 2). However, as the heterogeneity in this result is high (I^2 = 60%), we carried out a post hoc subgroup analysis showing results of the double-blind trials by decade of publication for the 2012 update (Figure 3). This shows that there is a tendency for the more recent studies to show more conservative results than the earlier studies. The studies published before 1990 (Peto OR 2.34; 95% CI 1.97 to 2.79) and between 1990 and 1999 (Peto OR 1.91; 95% CI 1.50 to 2.44) were more optimistic than those published since 2000 (Peto OR 1.24; 95% CI 1.01 to 1.54). It is also notable that the three studies with adequate allocation concealment (Decramer 2005; Schermer 2009; Zheng 2008) did not show large benefits of treatment on exacerbations. Furthermore, inspection of the new funnel plot in Figure 4 (for the 2012 update) indicates the possibility of 'small study' effects as there are no small studies showing negative outcomes. This raises the possibility that some negative small studies were not published, and publication bias could lead to overestimation of the benefits of treatment on exacerbations.

Figure 1. Forest plot of comparison: 1 Mucolytic versus placebo, outcome: 1.4 Patients with no exacerbations in study period.

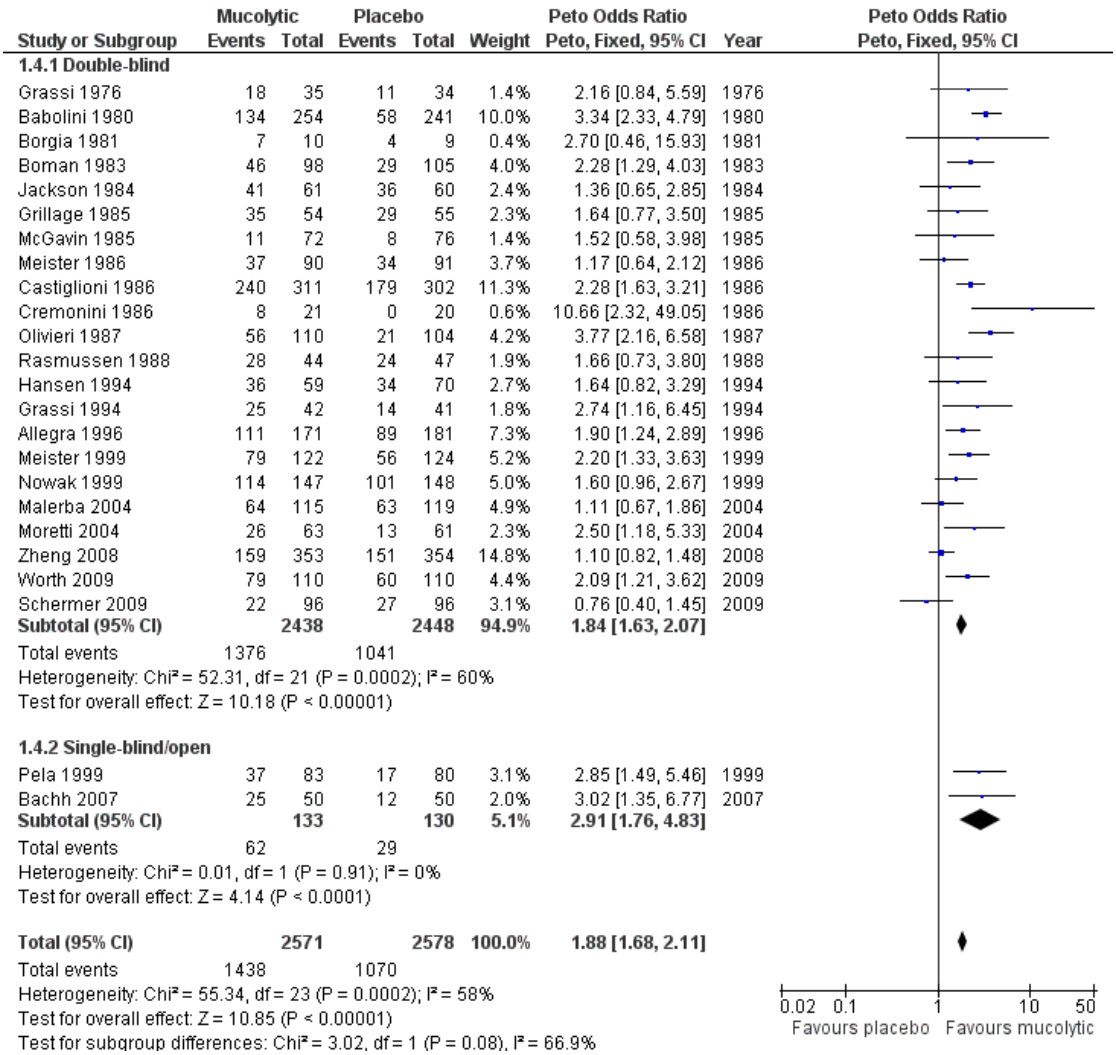


Figure 2. In the control group 58 people out of 100 had one or more exacerbations over 10 months, compared to 43 (95% CI 46 to 40) out of 100 for the active treatment group.

Figure 3. Forest plot of comparison: 1 Mucolytic versus placebo, outcome: 1.2 Patients with no exacerbation by decade.

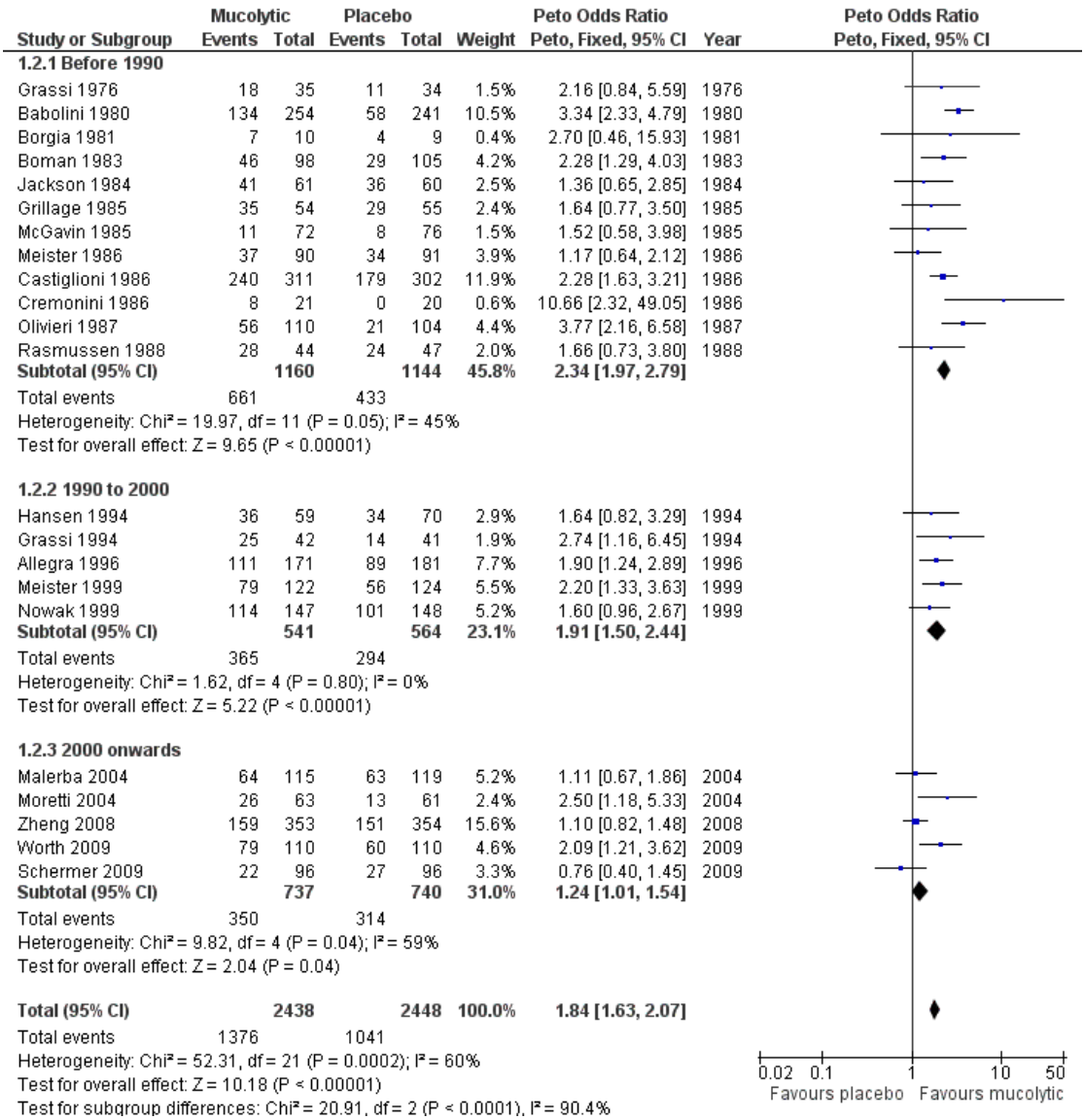
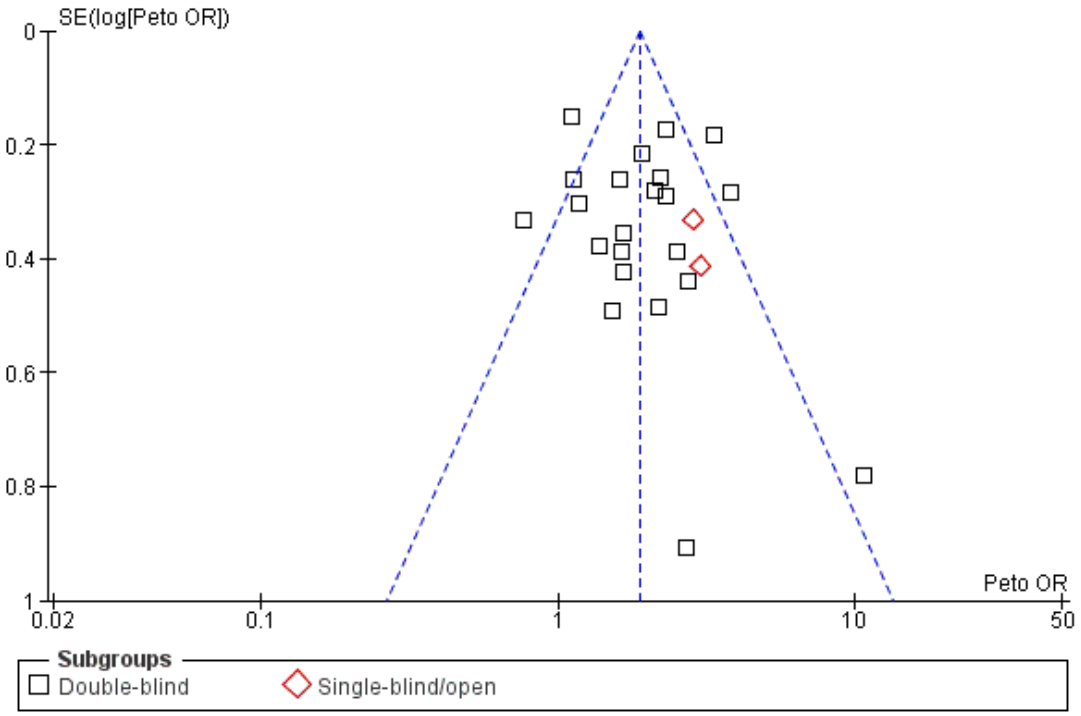


Figure 4. Funnel plot of comparison: 1 Mucolytic versus placebo, outcome: 1.4 Patients with no exacerbations in study period.



If the analysis is conducted only on those studies that were conducted for a period up to eight months over the winter, the effect is larger, with an odds ratio of 2.20 (95% CI 1.93 to 2.51, P < 0.00001; Analysis 1.5).

Number of exacerbations per patient per month

The use of mucolytics was associated with a reduction of 0.04 exacerbations per participant per month (95% CI -0.04 to -0.03; Analysis 1.3). These results need to be interpreted with caution as there was very high heterogeneity in this outcome (I^2 = 87%). One factor may relate to the scaling factors used for estimating the standard deviations of monthly exacerbation rates, which may have led to over precision in the estimates from each study. For this reason the monthly exacerbation results may be less reliable than those from the outcome above that assessed whether or not participants had an exacerbation.

Additionally, we were unable to include exacerbation data from a large American study in our review (Petty 1990). The paper stated that there was no significant difference in exacerbation rates between groups treated with iodinated glycerol or placebo, but no data were available on this outcome.

Parr 1987 had no measurement of error reported for their exacerbation rate. Owing to the large number of studies and the fact that this was a large study, we decided to assign it the pooled standard deviation (SD). If Parr 1987 is excluded, there is no change in the effect size. Malerba 2004 also made no mention of the SD, but did report the number with no exacerbations and the total number of exacerbations from which the mean was calculated. A very conservative estimate of the SD has been applied (approximately 10 times that which would be obtained if the rest of the participants had one, two or three exacerbations in a skewed distribution in the ratio 64%:32%:4%).

In contrast to the results for mucolytics, there was no significant reduction in exacerbation rates with the thiol donor N-isobutyryl-

cysteine (NIC). If NIC is added to the main analysis, there is no change in the overall effect size.

Exacerbations in patients not on inhaled corticosteroids (ICS)

An analysis of studies which were defined or stratified by non-use of concomitant ICS (Decramer 2005; Malerba 2004; Schermer 2009, see Analysis 1.8), found there was no significant difference in exacerbation rates between those treated with mucolytics and placebo (mean difference (MD) 0.02; 95% CI -0.01 to 0.04).

Time to first exacerbation

There are not yet sufficient data with which to perform a meta-analysis on this clinically relevant outcome. In a post hoc analysis of the EQUALIFE study (Ballabio 2008), patients on erdosteine had a significantly longer time until their first exacerbation compared with those on placebo, with a hazard ratio of 0.639 (95% CI 0.416 to 0.981). Longer time to first exacerbation was also reported by Nowak 1999. In that study, patients with chronic obstructive pulmonary disease (COPD) treated with N-acetylcysteine (NAC) had a mean of 139 days (SD 68) to first exacerbation compared with 108 (79) days for those on placebo ($P < 0.05$).

Number of days of disability per patient per month ('sick days')

There was a significant reduction of 0.48 days of disability per patient per month with mucolytic therapy (95% CI -0.65 to -0.30; Analysis 1.12).

Moretti 2004 did not report total 'sick days'; however, they reported that 10/63 in the erdosteine-treated group were hospitalised, compared with 19/61 in the placebo group (55% fewer, $P = 0.040$). They also reported the number of individuals losing workdays: seven in the erdosteine group and 10 in the placebo group, for a mean number of days lost per person of 0.8 and 1.1, respectively. This outcome applied therefore to 17/124 participants in the study. If the data for days off work from this study are included in the meta-analysis, the overall effect becomes smaller but remains significant, with 0.08 fewer days of disability per patient per month (95% CI -0.10 to -0.06). On the other hand, if the days of hospitalisation are included, the result changes to a reduction of 0.03 days of disability per patient per month (95% CI -0.06 to 0.00).

In the three studies that reported it, there was a mean reduction of 0.53 days on antibiotics per patient per month (95% CI -0.76 to -0.31; Analysis 1.13). In Meister 1999, in the myrtol-treated participants, significantly fewer patients with exacerbations required antibiotic therapy, and of those who did, the courses were shorter than those on placebo. Malerba 2004 reported no difference between ambroxol and placebo in terms of duration of courses of antibiotic treatments, working days lost or number of days of hospitalisation (no data given). Moretti 2007 used a post hoc analyses to report that erdosteine use was associated with relatively fewer antibiotic courses (32%) and shorter durations of treatment (15%) than placebo. The mean number of antibiotic courses per patient treated with erdosteine was also lower than for placebo (0.5 (SD 0.7) versus 0.7 (SD 0.7), $P = 0.045$).

In Meister 1999, 16/31 (52%) patients with exacerbations in the myrtol group needed antibiotics, compared with 30/49 (61%) of the placebo group, and the antibiotic courses were longer in the placebo group. The percentage of participants who needed antibiotics for more than seven days was 37% in the myrtol group and 77% in the placebo group.

Health-related quality of life

While many studies reported patient and/or physician global assessments of well-being, only five have used validated tools for evaluating health-related quality of life in COPD patients. In four studies the tool used was the St George's Respiratory Questionnaire (SGRQ, Jones 1992); in one it was the Chronic Respiratory Questionnaire (CRQ, Guyatt 1987).

We have combined total scores on the SGRQ at the end of the treatment period for three of these studies (Analysis 1.14). This shows a significant effect in favour of mucolytics when a fixed-effect model is used (MD -3.13; 95% CI -5.37 to -0.88), but not when a random-effects model is applied (MD -3.62; 95% CI -8.04 to 0.81) as there is considerable heterogeneity among the studies ($I^2 = 72\%$). Neither model results in an effect size that meets the minimum clinically important difference of 4 units on the SGRQ (Jones 2005).

The analysis includes data from the three-year Decramer 2005 study of 600 mg NAC daily, in which participants were evaluated with the SGRQ, although for technical reasons only about 80% of participants completed the questionnaire. During the first year of the study, participants in both the treatment and the placebo group improved their scores on both scales significantly, with no significant difference between the groups (-3.76 units on NAC and -4.95 units on placebo, difference between groups 1.18, $P = 0.358$, as reported in the text of the paper). In the second year this improvement tailed off again with no difference between treatment groups. More participants on placebo withdrew from the trial, and dropouts had a worse SGRQ score than those who remained in the study. We have used data provided by the authors from the mixed-effects model used in this study.

In Zheng 2008 the baseline SGRQ scores in the groups were well-matched. After 12 months of treatment, there were changes in SGRQ total scores from baseline amounting to -4.06 units in the carbocysteine group and -0.05 in the placebo group, but this did not represent a statistically significant difference between the groups ($P = 0.13$). There was a very large difference between the SGRQ symptom domain results between the carbocysteine group (-11.34 units) and placebo (-3.54 units), $P = 0.004$, in this study

which is unexplained. The results from the single measurement at one year in this study contrast to the multiple measurements taken in Decramer 2005, where no significant difference between the symptom score was found over time between NAC and placebo.
In the Worth 2009 study, the mean score change at six months from baseline was -4.3 in the placebo group and -9.9 in the cineole group (P = 0.06). However, we judged this study to be at high risk of selection bias.
In the eight-month Moretti 2004 study of erdosteine, participants completed both the SF-36 and the SGRQ. In the erdosteine-treated group, there was a significant improvement in all domains of the SGRQ, and in the total score, with no reported difference between the treated and the placebo groups. Data were therefore not suitable for inclusion in Analysis 1.14.
In the three-year study of NAC versus placebo (Schermer 2009), the CRQ was used. The groups were well-matched at baseline, with an improvement seen in both groups, particularly over the first year, but this never exceeded the 0.5 unit threshold regarded as clinically significant (Guyatt 1987). At the end of the study, there was no significant difference in CRQ total scores between groups (P = 0.306).
Thus, it seems that the overall evidence relating to health-related quality of life shows considerable variation among the studies that report it, which is currently unexplained.

Hospitalisation in the study period

There were comparative data available only from two recent studies (Decramer 2005; Moretti 2004). The odds ratio (OR) for hospitalisation with mucolytic treatment compared with placebo was 0.70 (95% CI 0.49 to 1.01; Analysis 1.15). Malerba 2004 reported no significant difference in hospitalisation rates but did not provide data. Bachh 2007 also reported a significant reduction (P < 0.05) in hospitalisations with four months of NAC, with 55 hospitalisations in 50 patients in the control group but only 37 in the 50 in the treated group. As it stands, these data cannot be included in the meta-analysis as the number of events in the control group exceeds the number of patients. If a conservative estimate of hospitalisations in the control group is made by entering them as 50 (not 55), the OR becomes significant (OR 0.59; 95% CI 0.42 to 0.84).
Days in hospital were reported by Moretti 2004. In this study, patients on erdosteine spent 70 days in hospital, compared with 163 in the placebo group (P = 0.04). This was a mean of 1.1 days per treated patient compared with 2.7 days per control patient.

Lung function

All studies that reported a simple measure of airways obstruction are combined in the outcome forced expiratory volume in one second (FEV_1) or %FEV_1 or peak expiratory flow rate (PEFR). This shows a significant difference at the end of treatment between mucolytic and placebo-treated patients in favour of mucolytic therapy (standardised mean difference (SMD) 0.12; 95% CI 0.03 to 0.21; Analysis 1.16). There is significant heterogeneity in this result so it must be interpreted with caution.
This analysis includes data from the Moretti 2004 study that reported a significant difference (> 300 mL) at the end of the study between the mucolytic and placebo groups, however the mucolytic group had higher baseline lung function and the net change was, therefore, closer to 200 mL. If this study is removed from the analysis there is no longer a significant difference in between the groups and the heterogeneity is removed.
There was no significant difference in forced vital capacity (FVC) at the end of the study period between patients treated with mucolytic and those with placebo (Analysis 1.17).
In the BRONCUS study of Decramer 2005, there was no reported difference between the NAC and placebo-treated groups over three years in terms of FEV_1, FVC or Diffusing capacity of the lung for carbon monoxide (DLCO) decline. FEV_1 declines were 54 mL and 47 mL, respectively, in the two groups. The authors did report a possible benefit of NAC on functional residual capacity (FRC), with a greater reduction in this measure. The difference was -0.374 litres (SD 1.03) P < 0.01) in NAC-treated patients, whereas for those treated with placebo there was only a 0.008 litre decrease. Moreover, the other three-year study (Schermer 2009) also found no difference between groups in lung function at the end of the study. In the NAC-treated group, FEV_1 declined 64 mL and in the placebo group, 60 mL. Decline in FVC was 79 mL and 65 mL, respectively.
In the other large well-conducted RCT of Zheng 2008, mean post-bronchodilator FEV_1 and oxygen saturations at the end of the study were not significantly different between those in the placebo and carbocysteine-treated groups. Malerba 2004 also reported no differences in simple lung function over a one-year study of ambroxol versus placebo, although no data were given.
In summary, it is likely that mucolytics do not affect disease progression in chronic bronchitis or COPD.

Adverse effects

The meta-analysis of adverse effects shows a significant effect in favour of mucolytic treatment, but with some heterogeneity (Peto OR 0.82; 95% CI 0.71 to 0.95, I^2 = 36%; Analysis 1.18). A sensitivity analysis using random-effects does not show a significant reduction in adverse effects (OR 0.83; 95% CI 0.69 to 1.01). Moreover, this analysis does not include data from several large studies. In Parr 1987 there were 1263 events in 258 participants in the mucolytics group (mean 4.9 per participant) and 1202 events in 268 participants (mean 4.5 per participant) in the placebo group. In Decramer 2005 there were 1428 events in 256 participants in the mucolytics group (mean 5.58 per participant) and 1381 events in 267 participants (mean 5.17 per participant) in the placebo group. None were thought to be drug-related. Similar numbers in each group were admitted to hospital (55 and 69, respectively). In

another study (Rasmussen 1988) there were 54 events in 59 participants in the mucolytic group and 66 events in 57 participants in the placebo group. In Meister 1999 there were 201 adverse effects in 122 participants in the mucolytic group (1.65 per participant) and 170 adverse effects in 124 participants in the placebo group (1.37 per participant). These studies could not be included in the meta-analysis because the event rates exceeded the numbers in the treatment groups. Malerba 2004 also reported no greater risk of events, or severity of events with mucolytic compared with placebo.

In summary, there is probably no difference between mucolytic and placebo treatments in terms of the total number of adverse effects they cause.

Deaths

Six studies reported on numbers of deaths in the mucolytic-treated and placebo groups. There was no significant difference seen (Peto OR 0.75; 95% CI 0.35 to 1.64; Analysis 1.19). As there were no deaths reported in either group in Zheng 2008, this could not be incorporated into the meta-analysis.

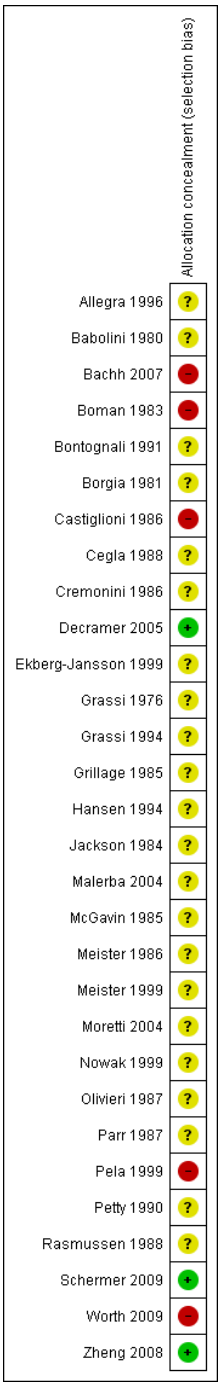
DISCUSSION

Summary of main results

2012 update

This latest update includes two new studies (Schermer 2009; Worth 2009) which did not markedly change the previous findings in relation to exacerbations. However, when we performed a post hoc investigation comparing the recent study results to those from previous decades, there was a clear reduction in the effect of treatment in the more recent studies (see Figure 3). Although the studies included in this analysis were double-blind, the older studies were more at risk of selection bias (see Figure 5), which may have led to an overestimate in treatment effect in these studies. Therefore we have a reduced level of confidence in the overall treatment effect estimate that seven additional participants would need to be treated over 10 months with mucolytics to keep an additional participant free from exacerbations (NNTB 7; 95% confidence interval (CI) 6 to 9). No significant difference was found in adverse events or mortality (see Summary of findings for the main comparison)

Figure 5. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Schermer 2009 is the first study to have found an increased number of exacerbations in the mucolytic-treated group compared with placebo; however this difference was not statistically significant. The exacerbation rate was generally low in this study and data were skewed by two patients in the N-acetylcysteine (NAC)-treated group who had very frequent exacerbations. Additionally, the study had a high dropout rate (43%).

Summary of previous findings

This review demonstrates overall small but statistically significant effects of mucolytics on exacerbations in patients with chronic bronchitis (21 studies) and chronic obstructive pulmonary disease (COPD) (eight studies), chronic bronchitis or COPD (one study). This is shown in terms of the mucolytic-treated groups being nearly twice as likely to be exacerbation-free during the study period, and to have about 0.04 exacerbations fewer per participant per month. This a 17% reduction in the number of exacerbations compared to the control group. If one considers the annualised exacerbation rate (weighted for study size) of 2.3 per patient per year in the control group, mucolytic treatment was associated with a reduction of about 0.4 exacerbations per patient per year, or one every two to three years. Consistent with this decrease in exacerbations was the finding that treatment with mucolytics also reduced days of disability. Of the secondary outcomes, mucolytics had no effects on any of them, with the possible exception of a small, but clinically marginal, improvement in health-related quality of life as measured by the St George's Respiratory Questionnaire (SGRQ). The observation that there were significantly fewer, or no, differences in exacerbation rates with mucolytic therapy was consistent and observed in all studies. For this outcome, however, there is significant heterogeneity among the studies and therefore the results do need to be interpreted with particular caution. To explore the causes for this heterogeneity, we divided the studies according to: baseline forced expiratory volume in one second (FEV_1 (as % predicted), type of mucolytic, dose of mucolytic, whether participants were included because they had a history of exacerbations, duration of therapy, whether concomitant inhaled steroids were used and the country in which the study was conducted. There was non-significant heterogeneity only in the two studies in which FEV_1 was less than 50% predicted and among the studies that reported those with no exacerbation in the study period - winter treatment only.

There is also the suggestion that exacerbations that do occur are either less serious or less prolonged. The effect of mucolytics on days of disability (-0.48 days per patient per month) was greater than the effect on number of exacerbations. This finding was based on a smaller number of studies (12) although there was some heterogeneity between them (Chi^2 = 19.7, df 7, P = 0.06, I^2 = 64%). However, there were four other studies with mean values reported (but no standard deviation (SD)), and these all showed a reduction in days of disability with mucolytics that was between 0.3 and 3.9 days per patient per month. The effect size of this significant reduction is smaller if the Moretti study is include in the analysis.

To provide some context for the interpretation of findings in this review, the ISOLDE trial, which treated moderately severe COPD patients with either 500 micrograms of fluticasone dipropionate twice daily for three years, or placebo, showed a reduction in exacerbations with fluticasone from 1.32 per year to 0.99 per year - an absolute reduction of 0.33 exacerbations per year, or 25% (Burge 2000). We found that mucolytics might be associated with up to 0.4 fewer exacerbations per year, or 17% fewer events.

There are theoretical reasons why mucolytics may modify disease in ways other than by reducing exacerbations: i.e. through antioxidant and thiol donor effects. More recent studies have aimed to explore whether or not the decline in FEV_1 over time is changed with mucolytics. The reduction in exacerbation rates with NAC was virtually identical to that observed with the other mucolytics, when they were examined as a group. The mechanisms responsible for the benefits of mucolytic treatment on exacerbation rates and days of disability cannot be determined from this review. However, the lack of an effect with N-isobutyrylcysteine (NIC) (a thiol donor with antioxidant properties) on exacerbation rates or days sick, raises the possibility that the actions of NAC as a thiol donor are less important in the reduction of exacerbations.

Despite the suggestion of a benefit from earlier trials, none of the large studies (BRONCUS study, PEACE study or COOPT study) showed any significant slowing of the decline in FEV_1 with mucolytic treatment. On the other hand, there is no evidence that mucolytics are unsafe, and they do not adversely affect quality of life, even though medicines need to be taken at least once a day.

Overall completeness and applicability of evidence

This review has now been updated five times. Over time, with a steady increase in the numbers of studies published, even though there has always been a significant treatment effect of mucolytics on exacerbations observed, the size of this effect has decreased almost 50% from the original report. This trend may be observed in Figure 3, where the studies have been ordered by year of publication and separated into decade of publication.

We have considered below two factors that may be contributing to this observation:

1. Improved study design, execution and

reporting over the years

There are narrower confidence intervals and consequently greater weight afforded to more recent studies. The forest plot in Figure 3 has been arranged by date and shows this trend. Part of the explanation is that the more recent studies have, on average, been larger than earlier ones. Another consideration is that there might have been publication bias in the reporting of results of earlier trials. This is suggested by an asymmetric funnel plot of Analysis 1.4 (Figure 4). We have persisted with using the more conservative fixed-effect model which gives greater weighting to recent larger studies such as Zheng 2008 and Decramer 2005. If a random-effects model is used, the effect size of mucolytic therapy is larger with a mean difference (MD) of -0.07 and 95% CI -0.09 to -0.05, but the degree of heterogeneity remains.

Another consideration is that tighter definitions of COPD have been used in later studies, which have generally included patients with, at most, moderate disease. To be included in earlier studies, patients only needed to have symptoms of chronic bronchitis. Additionally, later studies have been longer so may be more robust in ascertaining mean exacerbation rates. Finally, as mentioned previously, the older studies may be at more risk of selection bias, and this could have inflated the estimates of the treatment effect.

Furthermore, with longer studies, there may be an element of 'immortal time bias' introduced though exposure time being longer in the intervention group (through fewer dropouts) than in the placebo group (more dropouts). This would allow more exacerbations to be recorded in those remaining in the study, hence diluting any treatment effect. This bias may have contributed to our finding that the effect of mucolytic treatment was greater in studies of less than three months than in studies more than three months long (see Analysis 1.9).

2. Improved COPD care

Comprehensive management of COPD includes support for smoking cessation, vaccination, pulmonary rehabilitation and use of inhaled corticosteroids and long-acting beta-agonists and anticholinergic agents (GOLD 2011), each of which may impact on exacerbation frequency or severity.

If the exacerbation rates were lower in more recent studies, then there would be less room for improvement with mucolytics. In support for this, there were lower monthly exacerbation rates in the control groups of studies reported since 2000 (0.11 exacerbations per participant per month), compared with 0.28 per participant per month before 1990 and 0.36 between 1990 and 2000 (derived from Analysis 1.3). On the other hand, the likelihood of being exacerbation-free in the control groups did not show such a trend, being 38% in pre-1990 studies, 52% between 1990 and 2000, and 42% since 2000 (derived from Analysis 1.2).

Inhaled steroids (ICS) have been available for asthma since the late 1970s but it is unlikely they were used by the chronic bronchitis participants in the trials before 1990. In most of the other studies, ICS were allowed. There are now data from five studies that address the relative effects of mucolytics and ICS. Malerba 2004 specifically excluded those on ICS and Decramer 2005 reported results for the subgroup not on ICS. Based on the report of average lung function, the participants in these two studies had relatively mild COPD. The weighted annual event rate in the relevant placebo groups of these two studies was 1.04, yielding a 17% reduction in exacerbations with mucolytics. The effect of mucolytics in the non ICS patients in these two studies was a MD of around -0.21 exacerbations per year, or -0.02 per month compared with placebo. This is about half that seen when all the mucolytic studies are combined. It is difficult to know what to make of this observation as the numbers are small and involve two different mucolytics, NAC and ambroxol. Moreover it is not clear from the trial reports whether these were post hoc subgroup analyses.

In Zheng 2008 only 17% of patients were on inhaled steroids (compared with 70% in Decramer 2005), but these investigators found no differences in effect of carbocysteine between those taking or not taking concomitant inhaled steroids. They did suggest the doses of ICS would have been low in this small group of patients; findings not necessarily at odds with the Decramer study. On the other hand, the Schermer 2009 study was designed to compare fluticasone, NAC and placebo. In contrast to every other study in this review, the exacerbation rate was higher (1.35 times) with NAC than placebo, but this did not reach statistical significance (P = 0.054). They also found the exacerbation rate 1.30 times higher with fluticasone (P = 0.095), suggesting that effect sizes were similar between NAC and fluticasone. Because of the methodological issues with this study, including high dropout rates and skewed exacerbation rates, it is difficult to be certain about this.

In summary, earlier studies of participants not on ICS (as they were not available) show an effect with mucolytics, in contrast to later studies of participants stratified as not being on ICS which do not.

Quality of the evidence

Although the trials included in this review were almost all double-blind, there were only three studies that had clearly concealed allocation (Decramer 2005; Schermer 2009; Zheng 2008). In combination with the time trends (less optimistic results in the more recent trials), the possibility of publication bias seen in the funnel plot (Figure 4), and the high and unbalanced dropout rates in some of the longer trials (e.g. Decramer 2005), this means that the overall risk of bias inflating these trial results is high. Thus further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Potential biases in the review process

The subgroup analysis by decade of publication is post hoc for the 2012 update and we have therefore not assessed the likelihood that the differences between subgroups have arisen by chance.

In Analysis 1.3, which examined the monthly exacerbation rate, we imputed some standard deviations. This could have narrowed the confidence intervals for the individual studies and thus increased heterogeneity. Furthermore, the approach we used may tend to overestimate the number of exacerbations per year in both groups as more occur during the winter months when many of these studies were performed.

Despite a consistent approach being used, there may have been slight rounding errors introduced by the calculation of exacerbation rates per participant per month from study data to fit into earlier versions of RevMan that allowed only two decimal points.

Agreements and disagreements with other studies or reviews

In addition to this review, there have been two other systematic reviews of the effects of NAC in chronic bronchitis reported. Our results are consistent with these. The larger of these included 11 randomised controlled trials (RCTs) (Stey 2000). Overall, those treated with NAC were more likely to remain exacerbation-free (OR 1.56; 95% CI 1.37 to 1.77), with a NNT of 6 (95% CI 5 to 9). Participants were more likely to report an improvement in symptoms with NAC (OR 1.78; 95% CI 1.54 to 2.05) than with placebo. The second review analysed nine trials that had been included in both the Stey 2000 and this Cochrane Review and confirmed the significant effect on exacerbations (SMD -1.37; 95% CI -1.5 to -1.25) (Grandjean 2000).

A retrospective cost-effectiveness analysis of NAC in chronic bronchitis has been performed (Grandjean 2000a), based on direct costs of NAC treatment, management of an acute exacerbation and indirect costs of sick leave. This suggested that the point at which the costs of treatment and non-treatment were equal was a reduction of 0.6 exacerbations per six-month period. In our review, there was a reduction of about 0.24 per six-month period suggesting that it would not be cost-effective to treat everyone with COPD with mucolytics.

Bachh 2007 and colleagues from India estimated the cost of prophylactic NAC therapy to be INR 6000 (USD 120), whereas a short course of oral steroids and antibiotics to be INR 200 (USD 4). ICSs are also expensive. As the burden of COPD over the next decades is going to disproportionately affect developing nations, the relative costs of each strategy are important to determine.

The analyses in this review suggest that mucolytics might, in addition, have an effect on duration and severity of exacerbations that do occur, and the likelihood of taking antibiotics. Data from three recent studies suggest that mucolytics are associated with decreased hospitalisation rates. It would be helpful if future studies looked at this outcome as this is where the bulk of costs associated with more severe disease arise. Few other pharmacological treatments have been shown to reduce hospitalisation: an immunomodulatory agent OM-85 BV, or Broncho-Vaxom (Collet 1997), was shown in COPD to reduce the number of hospital admissions even though it did not affect the number of exacerbations.

AUTHORS' CONCLUSIONS

Implications for practice

Mucolytics may reduce the number of exacerbations in people with chronic bronchitis or chronic obstructive pulmonary disease (COPD) by a small amount, but do not appear to cause any harm. If they do, the reduction is at most one fewer exacerbation every two years. One person in seven may avoid having an exacerbation provided they all take treatment every day for an average of 10 months. Mucolytics have not been shown to slow the decline in lung function, nor improve quality of life. As reduction in exacerbations seems the only potential benefit, mucolytics might be considered as a treatment option in patients with frequent exacerbations who cannot take any other therapies such as inhaled corticosteroids or long-acting bronchodilators, which have a stronger evidence base for their effectiveness. It is not clear whether or not they have any effect when used as add-on treatment to other therapies used to reduce exacerbations.

Implications for research

Future studies might address the value of mucolytic therapy:

- in patients who have multiple exacerbations per year, or who have prolonged or severe exacerbations; and
- in patients with repeated admissions to hospital with exacerbations of COPD.

Studies should stratify participants by whether or not they are taking concomitant inhaled corticosteroids (ICS) or long-acting bronchodilators.

Outcomes of studies should include hospitalisations, mortality, numbers of days sick, forced expiratory volume in one second (FEV_1) and a validated measure of quality of life.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Allegra 1996

Methods	Randomised, DB, PC, parallel, multicentre, with 1 month run-in before randomisation. Duration 6 months. ITT (intention-to-treat) and PP (per protocol) analysis
Participants	242 participants, with COPD (ATS definition) and chronic bronchitis. Age 40 to 75, FEV_1 60% to 80% (GOLD stage IIA), pathological chest auscultatory findings and at least 1 exacerbation in previous 12 months Exclusions: CF, bronchiectasis, asthma, centrilobular emphysema, peptic ulcer or liver, kidney or heart insufficiency Other mucoactive and anti-cough agents, oral or inhaled corticosteroids not permitted. ICS withdrawn at least 4 weeks prior to study. Mean age 60 years, 75% had smoking history, FEV_1 2.12 (SD 0.6) litres, mean 2.7 (SD 1.3) exacerbations in last 12 months. Dropouts: 34 (16%)
Interventions	Three treatment arms. Carbocysteine lysine salt monohydrate (SCMC-Lys) 2.7g daily, placebo and SCMC-Lys 2.7 g daily alternating week active, one week placebo. We assessed continuous versus placebo treatment only
Outcomes	Diary scores of symptoms, exacerbations, time to first exacerbation, duration of exacerbation, days on antibiotics, adverse events
Notes	Italian. Requested SD for exacerbations per protocol and intention-to-treat analysis. The requested data were provided by the sponsoring company. Intention-to-treat analysis was used with an estimate of duration of treatment derived from the paper. Jadad score 5

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available

Babolini 1980

Methods	DB, PC, parallel, 36 centres. PP analysis. Duration 6 months
Participants	744 outpatients with chronic bronchitis defined by MRC. Excluded if too young, too sick, additional significant disease, history of peptic ulcer, on mucolytics. 60% were over the age of 50, 73.5% male, mean FEV_1 2.18 litres, FEV_1 40% to 70% predicted, 64.3% smokers. 249 dropouts. Baseline groups matched. Dropout groups matched
Interventions	NAC 200 mg bd or placebo

Babolini 1980 (*Continued*)

Outcomes	Exacerbations, symptom scores, global assessments by patients and physicians, adverse effects, days on antibiotics
Notes	Italian. Same data also in Ferrari. SD calculated from graph. Five or more exacerbations counted as 5. Further data requested, not yet provided. Jadad score 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available

Bachh 2007

Methods	Randomised, single-blind, PC, parallel, single centre. Follow-up 12 months, although treatment only given for 4 months
Participants	100 outpatients with smoking-related COPD. Age > 50 years, post-bronchodilator FEV_1 30% to 80% predicted, reversibility < 12%, FEV_1/FVC < 70%. Stable medications and inhaled corticosteroids permitted at steady dose. Exclusions: intolerance of NAC, continuous treatment with oral steroids, NAC for 3/12 or more, asthma or atopy, other respiratory diseases, NYHA Class 2 or more heart failure. Non compliance in taking medication Mean age: 61 (SD 7) years, 78% male. Mean duration of disease 6.4 years. Mean number of exacerbations in 2 years prior to study, 4.7. Mean FEV_1 52% (SD 10) predicted and reversibility 6% (SD3). 18/100 (18%) were using ICS No dropouts recorded.
Interventions	NAC 600 mg once daily or placebo for 4 months
Outcomes	Exacerbations, hospital admissions, pulmonary function tests, adverse effects
Notes	Indian study Jadad score 0

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	

Boman 1983

Methods	Randomised, DB, PC, parallel, run-in, multicentre. Duration 6 months
Participants	259 outpatients with chronic bronchitis defined by MRC. Exclusion criteria asthma, FEV_1 < 50%, other co-morbidities, on antibiotics, women pregnant or trying for pregnancy. 56 dropouts. Mean age 51.9 years. FEV_1 80% of predicted. 100% smokers. Had exacerbations in last 12 months
Interventions	NAC 200 mg bd or placebo
Outcomes	Exacerbations, sick leave due to exacerbations, adverse effects
Notes	Swedish. SD calculated from paper. Six or more exacerbations counted as 6. Requested more information to calculate effect on sick days but authors unable to locate original material. Jadad score 2

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	Investigators aware as to order of allocation

Bontognali 1991

Methods	Randomised DB, PC. Duration 3 months.
Participants	60 participants recruited as inpatients. 63% male. Mean age 57 years. Admission criteria of 20 ml sputum/day with a history of 4 or more episodes of acute bronchitis in last 12 months and Tiffeneau index of 40% or less. No loss to follow-up
Interventions	Cithiolone 400 mg bd or placebo for 1 month followed by 400 mg od for a further 2 months
Outcomes	Exacerbations and duration of acute exacerbations, FEV_1 and FVC, sputum viscosity, adverse effects
Notes	Italian. Surprisingly, none withdrawn in course of study. Huge confidence limits. There may be a typographical error in the paper, as the SD for the number of exacerbations per month is the same as for the duration of the exacerbations. We have used the authors rates in comparison 01:02 and divided them by months for comparison 01:01. Jadad score 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available

Borgia 1981

Methods	Randomised, DB, PC, parallel, multicentre. PP analysis. Duration 6 months
Participants	21 outpatient with chronic bronchitis defined by MRC, and an exacerbation in the period before the study. Mean age 45.3 years and FEV_1 3.82 litres. Exclusions not stated except FEV_1 less than 40%. 2 dropped out.
Interventions	NAC 200 mg bd or placebo
Outcomes	Exacerbations, lung function, symptom scores, clinical assessment, adverse effects
Notes	Italian and published in Italian therefore reliant on translation. Large difference in baseline rates for lung function. Jadad score 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available

Castiglioni 1986

Methods	Randomised, DB, PC, parallel, multicentre (18). PP analysis. Duration 3 months
Participants	706 outpatients with chronic bronchitis defined by MRC. Mean age 56.5 years, 76% male, FEV_1 73.3% predicted, 73.5% current or former smokers. Excluded were patients under 18 or over 75, FEV_1 under 60%, severe comorbidity, prior treatment with oral corticosteroids, or antibiotics, and more than 2 other medications. 33 dropped out
Interventions	Sobrerol 300 mg bd or placebo
Outcomes	Exacerbation rate, consumption of antibiotics and other medicines, clinical signs, laboratory data, lung function, global assessment by investigator and patient, adverse effects
Notes	Italian. Requested more information to be able to determine days on antibiotics, not yet provided. Jadad score 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	Investigators aware as to order of allocation

Cegla 1988

Methods	Randomised, DB, PC, parallel, multicentre. PP analysis. Duration 24 months
Participants	180 outpatients with chronic bronchitis defined by WHO Mean age 51.1 years, 64% male, mean FEV_1 2.15 L, 36% current smokers. Excluded were patients over 60 years, patients with asthma, cor pulmonale, pulmonary hypertension or polycythaemia under 60%. 23 dropped out. 4 died
Interventions	Ambroxol retard 75 mg daily or placebo
Outcomes	Exacerbations, days sick (off work, in hospital) patient symptoms by diary card, lung function, extra medication use, assessment by investigator and patient, adverse effects
Notes	German. Written in German. required translation. Jadad score 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available

Cremonini 1986

Methods	Randomised, DB, PC, parallel. Duration 3 months.
Participants	41 outpatients with chronic bronchitis defined by ERS, all of whom completed the study. Exclusion criteria not stated. Mean age 60.8 years, FEV_1 58.6% predicted.
Interventions	Letosteine 50 mg tds or placebo
Outcomes	Exacerbations, days off work sick, lung function. Adverse effects not evaluated
Notes	Italian, written in Italian therefore relying on translation. SD calculated from raw data in paper, but numbers in placebo and active group vary (20/21 or 21/20 respectively) Jadad score 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available

Decramer 2005

Methods	Randomised, DB, PC, parallel, multicentre. ITT analysis. Duration 3 years
Participants	523 outpatients with smoking-related COPD. Age 40 to 75 years, post-bronchodilator FEV_1 40% to 70% predicted, reversibility < 12% and 200 ml, FEV_1/FVC , 88% for men and 89% for women and history of at least 2 exacerbations during the 2 years before enrolment. Exclusions: intolerance of NAC, continuous treatment with oral steroids, NAC for 3/12 or more, asthma or atopy, other respiratory diseases, NYHA Class 2 or more heart failure, GI disease, likely LTOT or lung transplant, alpha 1 antitrypsin deficiency, enrolment in rehab or other study 3 months prior to this study. ICS permitted although steady dose recommended Mean age: 62 (SD 8) years, 79% male, FEV_1 1.65 (SD 0.38) litres, 57% (SD 9) predicted. 46% current smokers, 70% used ICS. Yearly exacerbation rate (control group) 2.5 (SD 0. 9) events Dropouts: 70 (27%) in NAC group and 99 (37%) in placebo group (P = 0.018)
Interventions	NAC 600 mg daily versus placebo
Outcomes	Yearly reduction in lung function and exacerbation rate Secondary endpoints: quality of life and cost utility Planned subgroup analyses - by baseline ICS dose and disease severity
Notes	European. BRONCUS study. Cost utility will be reported in another publication Jadad score 5 Data from the mixed-effects model used in this study have been provided by Professor De Cramer for total SGRQ scores. The change on NAC was -2.31 and on placebo -3.71. Add these to the baseline (using baseline SD) 36.7 (16) 36.3 (15) to get total SGRQ at end of study to enter into RevMan

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	Allocation concealed from study investigators

Ekberg-Jansson 1999

Methods	Randomised, DB, PC parallel, multicentre (41). PP analysis. Duration 6 months
Participants	637 outpatients with chronic bronchitis defined by MRC 1 exacerbation in previous winter. Average age 58 years, 61% male, mean FEV_1 73% predicted, 100% current or ex-smokers. Excluded were females of fertile age, FEV_1 < 40% predicted, significant reversibility, patients with unstable non respiratory disease, other respiratory disease, atopy, peptic ulcer, lactose intolerance or daily purulent sputum. 134 dropped out

Ekberg-Jansson 1999 (*Continued*)

Interventions	N-isobutyrylcysteine (NIC) 300 mg bd or placebo
Outcomes	Time to first exacerbation, exacerbation rate, days sick (judged by patients and investigators) , lung function, adverse effects
Notes	European including British. New agent-free thiol donor derivative of NAC. Jadad score 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available

Grassi 1976

Methods	Randomised, DB, PC, parallel, multicentre (6). PP analysis. Duration 6 months
Participants	80 outpatients with chronic bronchitis defined by American and British criteria. 11 dropped out. Mean age 60.9 years, 80% male
Interventions	NAC 600 mg daily or placebo for 3 days per week
Outcomes	Exacerbations, clinical symptoms (3 months), sputum characteristics, adverse effects
Notes	Italian. SD calculated from paper. Three or more exacerbations counted as 3. 1 to 2 exacerbations counted as 1.5. Jadad score 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available

Grassi 1994

Methods	Randomised, DB, PC, parallel, multicentre. PP analysis. Duration 3 months
Participants	135 outpatients with chronic bronchitis with at least 2 exacerbations in the previous winter randomised to one of 3 treatments. Participants aged 40 and 75, mean age 61.8 years, and had chronic bronchitis for at least 5 years. FEV_1 56.7% predicted, 76% smokers. For this analysis n = 87. 4 dropped out
Interventions	Carbocysteine-sobrerol 1 dose daily, placebo 1 dose daily or alternating active-placebo for 10 days each, for 3 months. One treatment group was intermittent and this is not included

Grassi 1994 (*Continued*)

	in the analysis	
Outcomes	Exacerbations, symptoms, sputum characteristics	
Notes	Italian and published in Italian therefore relying on translation. SD calculated from paper. Jadad score 4	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Information not available

Grillage 1985

Methods	Randomised, DB, PC, parallel, multicentre (17). PP analysis. Duration 6 months	
Participants	109 general practice patients with chronic bronchitis defined by MRC, reversibility < 20%. Exclusions were patients with severe hepatic or renal impairment, peptic ulcer or those on mucolytics or steroids. Participants were aged over 40 years, mean PEFR 232 L/min, and had episodes of bronchitis in previous winters. 11 dropped out including 2 who died	
Interventions	Carbocysteine 750 mg tds or placebo	
Outcomes	Exacerbations, lung function, adverse effects	
Notes	British. Excluded from original review but with new comparison "pts with no exacerbations", can now be included. Jadad score 4	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Information not available

Hansen 1994

Methods	Randomised, DB, PC, parallel, multicentre (6). 4 week run - in. PP analysis. Duration 5 months
Participants	153 outpatients with chronic bronchitis defined by MRC. With at least 2 exacerbations in the last year and FEV_1 at least 50% predicted and less than 20% reversibility. 100% had smoked. Exclusions were those with atopy, heart disease and on long-term antibiotics. Mean age 51.4 years, 43% male. Mean FEV_1 2.34 litres, 24 dropped out.
Interventions	NAC 600 mg bd or placebo

Hansen 1994 (*Continued*)

Outcomes	Exacerbations, subjective symptom scores, global well-being, lung function, adverse effects. Did not assess sick days	
Notes	Danish Jadad score 3	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Information not available

Jackson 1984

Methods	Randomised, DB, PC, parallel, multicentre (16). PP analysis. Duration 3 months	
Participants	155 general practice patients with chronic bronchitis defined by MRC. 88% had smoked. Exclusions were those with serious other respiratory disease, peptic ulcer, on long-term antibiotics or requiring mucolytics. Mean age 63 years, 67% male. 34 dropped out	
Interventions	NAC 200 mg tds or placebo	
Outcomes	Exacerbations, subjective symptom scores, clinical signs, radiological appearance, global well-being, adverse effects	
Notes	British. Excluded from original review but with new comparison "pts with no exacerbations", can now be included. Jadad score 4	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Information not available

Malerba 2004

Methods	Randomised, DB, PC, parallel multicentre (26). ITT and OT. Duration 12 months.
Participants	242 participants, with COPD (ATS definition) and chronic bronchitis. Age 40 to 75, FEV_1 60% to 80% (GOLD stage IIA), pathological chest auscultatory findings and at least 1 exacerbation in previous 12 months. Exclusions: CF, bronchiectasis, asthma, centrilobular emphysema, peptic ulcer or liver, kidney or heart insufficiency Other mucoactive and anti-cough agents, oral or inhaled corticosteroids not permitted.

Malerba 2004 (*Continued*)

	ICS withdrawn at least 4 weeks prior to study. Mean age 60 years, 75% had smoking history, FEV_1 2.12 (SD 0.6) litres, mean 2.7 (SD 1.3) exacerbations in last 12 months Dropouts: 34 (16%)	
Interventions	Ambroxol 75 mg bd or placebo	
Outcomes	Exacerbations over first 6 months (winter period) and at 12 months. Secondary: cough intensity and frequency, difficult expectoration, dyspnoea, days on antibiotics, no. of working days lost, and no. days of hospitalisation	
Notes	Italian, AMETHIST study Post hoc analysis on more severe patients Jadad score 2	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Information not available

McGavin 1985

Methods	Randomised, DB, PC, parallel, multicentre (26). PP analysis. Duration 5 months	
Participants	244 participants entered study with 200 participants randomised. 181 randomised appropriately (others ineligible or untraceable). Chronic bronchitis defined by MRC, one or more exacerbations per year for the last 3 years, FEV_1 less than 50% and FEV_1/VC less than 70% predicted. Mean FEV_1 was 0.86 litres. Mean age 63.4 years, 85% male. 99% were current or ex-smokers. 148 completed 5 months treatment	
Interventions	NAC 200 mg tds or placebo	
Outcomes	Exacerbations, days of antibiotics, days in bed, FEV_1 and VC, adverse effects	
Notes	British. BTS research committee. Mean exacerbation rate given by authors does not agree with what we calculated from their raw data. Have used authors rates. Have used SE from body of text (same value reported in abstract as SD). For post-treatment FEV_1, have estimated SD from baseline data. Jadad score 4	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Information not available

Meister 1986

Methods	Randomised, DB, PC, parallel, multicentre (54). PP analysis. Duration 6 months
Participants	252 outpatients with chronic bronchitis defined by WHO. At least 1 exacerbation in the last winter. 10 patients with asthma and chronic bronchitis were included. Exclusions were those who had had at least 14 days antibiotics for chronic bronchitis in past 6 months, pregnancy. Average age 57.2 years, 59% male. Average PEFR 303 L/min. 88% had smoked. 71 dropped out
Interventions	NAC 300 mg bd or placebo
Outcomes	Exacerbations, days sick, concomitant treatment, adverse effects
Notes	German. Study not published. Provided by Zambon. Jadad score 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available

Meister 1999

Methods	Randomised, DB, PC, parallel, multicentre (19). PP and ITT analysis reported. Duration 6 months
Participants	246 outpatients with chronic bronchitis as defined by WHO and FEV_1 > 50% predicted. 215 completed 6 months. At least 1 exacerbation in the last winter. Exclusions were those who had had antibiotics in past 2 months, peptic ulcer disease, neoplasia, allergy to essential oils, pregnancy, lactation, severe concomitant disease. Average age 57 years, 44% male. Mean FEV_1% predicted 78%. 55% had smoked. 42 dropped out.
Interventions	Myrtol 300 mg tds or placebo
Outcomes	Exacerbations, number of exacerbations requiring antibiotics, well-being, adverse effects
Notes	German. Abstract provided by Douglas Pharmaceuticals. Full paper (English) provided by Pohl-Boskamp. PP analysis used in review (participants completing 6 months). Results of ITT analysis consistent with PP analysis. Jadad score 4.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available

Moretti 2004

Methods	Randomised, DB, PC, parallel, multicentre (9). PP analysis reported. Duration 8 months
Participants	155 outpatients with COPD defined by ERS. Age 25 to 85 years; one or more exacerbations in previous winter; FEV_1 < 70% predicted; CXR no acute lung disease; smoking history > 20 pack-years; stable and at least 4 weeks since last exacerbation Exclusions: continuous treatment with oral steroids or expectorants; rapidly progressive bronchial disease; serious comorbidity; asthma; known poor compliance Mean age 67 years, 80% male, 33% smokers, FEV_1 after salbutamol 1.68 litres (SD 0.31) in erdosteine group and 1.59 (0.29) in placebo group Dropouts: 31/155 (20%). Equal in both groups and similar reasons. 63 completed in mucolytic group and 61 in placebo group
Interventions	Erdosteine 300 mg bd or placebo
Outcomes	Exacerbation frequency, duration, hospitalisation, lung function, 6-minute walk test, quality of life (St George's Respiratory Questionnaire), pharmacoeconomic analysis
Notes	Italian. EQUALIFE study. Mucolytic group had (insignificantly) more males and better lung function at baseline Jadad score 2

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Information not available

Nowak 1999

Methods	Randomised, DB, PC, parallel, multicentre (10 centres). PP analysis. Duration "long term" means 8 months
Participants	313 outpatients with COPD (? definition). Mean age 57 years, 60% male. Mean FEV_1 60% predicted. 18 dropped out.
Interventions	NAC 600 mg daily or placebo
Outcomes	Exacerbations, severity of exacerbations, time to first exacerbation, days sick, lung function. patient symptoms, adverse effects
Notes	European. COPD not chronic bronchitis. BREATHE study. Published in abstract from only. Zambon provided more information. Study to be published shortly Jadad score 2

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Nowak 1999 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Information not available

Olivieri 1987

Methods	Randomised, DB, PC, parallel, multicentre (13). PP analysis. Duration 6 months
Participants	240 outpatients with chronic bronchitis defined by MRC. Had at least 3 exacerbations in previous year or pathological auscultatory assessment or reduction of 15% to 40% in FEV_1. Exclusions were participants with asthma, FEV_1 less than 40% predicted, peptic ulcer or other serious comorbidity, pregnancy, on long-term antibiotics or mucolytics. 26 dropped out
Interventions	Ambroxol retard 75 mg or placebo daily
Outcomes	Exacerbations, courses of antibiotics, days sick, FEV_1, VC, symptoms, auscultatory findings, physician and patients' global assessments, laboratory data, adverse effects
Notes	Italian. We suspect what is reported as SD in the paper is in fact SE (using t statistic and P values). We have written to the authors for clarification. No reply received as yet. Jadad score 2

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Unclear risk	Information not available

Parr 1987

Methods	Randomised, DB, PC, parallel, multicentre. PP analysis. Duration 6 months
Participants	526 general practice patients with chronic bronchitis defined by MRC, with at least one exacerbation in the last 12 months. Patients were excluded for other significant respiratory disease, active peptic ulceration, severe heart failure, or continuous therapy with antibiotics or mucolytics. There were 204 dropouts. Mean age 63 years, 66% male, and 86% had smoked
Interventions	NAC 200 mg tds or placebo.
Outcomes	Exacerbations, days off work, adverse effects
Notes	British. Pharmaceutical company trial. Large number of dropouts, although seemed matched. SD calculated from raw data in the paper. Need more data to calculate days sick. Jadad score 4

Risk of bias

Parr 1987 (*Continued*)

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available

Pela 1999

Methods	Randomised, open, PC, parallel, multicentre (5). Duration 6 months. PP analysis
Participants	169 outpatients with COPD (defined by ATS and ERS), aged 40 to 75 years, FEV_1 < 70% predicted, reversibility < 12%. Exclusions were participants with lung cancer, cardiomyopathy, metabolic disease, renal failure, other severe disease. Mean age 66 years, 76% male, mean FEV_1 1.49 L, 58% predicted, 28% current smokers. 6 dropped out.
Interventions	NAC 600 mg daily or placebo
Outcomes	Exacerbations, exacerbation severity, days sick, patient preference, lung function
Notes	Italian study. Open study. COPD not chronic bronchitis. Jadad score 1

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	Investigators aware as to order of allocation

Petty 1990

Methods	Randomised, DB, PC, parallel, multicentre. Duration 2 months. ITT analysis
Participants	367 outpatients with stable chronic bronchitis defined by American Thoracic Society were randomised. Required pre-bronchodilator FEV_1 < 75% predicted. There were 79 dropouts (33 in mucolytic group and 46 in placebo group). Mean age 65 years, 70% male, mean FEV_1 44.5% predicted. Excluded were patients who were pregnant or lactating, allergic to iodine, with comorbidity that would confound response or compliance, with asthma, and those with exacerbation in past month. Patients using antibiotics or anticholinergics were excluded
Interventions	Iodinated glycerol 30 mg, 2 tabs 4 times a day or identical-looking placebo
Outcomes	Investigator assessment of symptoms, patient evaluation of symptoms, and global assessment at weeks 0, 4 and 8, frequency of bronchodilator use, number and duration of acute exacerbations, frequency of concomitant medications, adverse experiences. Dropouts were assessed at weeks 4 and 8

Petty 1990 (*Continued*)

Notes	American. Requested more information from author, but unable to provide. Pharmaceutical company (Wallace) approached. No reply. No significant difference (reported) between groups in exacerbation rates, however, significantly fewer days sick in treatment group. We have estimated sample SD from t statistic and pooled t formula, and assumed equal variances to arrive at an estimate for s of 18.8. Jadad score 5

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available

Rasmussen 1988

Methods	Randomised, DB, PC, parallel, multicentre (9). PP analysis. Duration 6 months
Participants	116 outpatients with chronic bronchitis defined by MRC. At least one exacerbation in previous winter. 100% had smoked. Mean age 58.9 years, 57% male and average PEFR of 305 litres/minute. 25 dropped out
Interventions	NAC 300 mg bd or placebo
Outcomes	Exacerbations, days sick evaluated by days on sick list and by patient diaries, adverse effects
Notes	Swedish Jadad score 3

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	Information not available

Schermer 2009

Methods	Randomised, DB, PC, parallel, multicentre (44 general practices). Duration 3 years. ITT and PP analysis
Participants	192 (in study arms NAC and placebo, each n = 96) GP outpatients with chronic bronchitis or stable COPD between the ages of 35 and 75. Patients current or former smokers; with chronic dyspnoea, sputum and cough for at least 3 consecutive months in previous 2 years; post-bronchodilator FEV_1 < 90% and/or post-bronchodilator FEV_1/FVC ratio < 0.88 for men and < 0.89 for women. Exclusions FEV_1/FVC ratio < 0.4 and/ or a history of asthma, allergic rhinitis or eczema There were 84 dropouts (44 in mucolytic group and 40 in placebo group). Mean age 59 years, 73% male, mean post-bronchodilator FEV_1 2.15 L (62% predicted). 53% were still

Schermer 2009 (*Continued*)

	smoking. 22% were chronic bronchitis with no obstruction, 14% mild, 47% moderate and 17% severe COPD. Mean CRQ score 4.84, baseline exacerbation rate mean 0.88 per year/median 0.5 Patients well-matched at baseline. High dropout rate. Generally low exacerbation rates, except a small number of patients who experienced very frequent exacerbations
Interventions	Three arms, double-dummy (tablet and inhaler). NAC 600 mg effervescent tablet daily versus fluticasone 500 µg bd versus placebo. This review only included NAC versus placebo arms. Two weeks of pre-treatment with prednisone 30 mg daily
Outcomes	Primary outcomes were: rate of exacerbations and disease-specific quality of life, as measured by CRQ Other outcomes were lung function and hospitalisation
Notes	Jadad score 5

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	

Worth 2009

Methods	Randomised, DB, PC, parallel, multicentre (11 centres - 4 GPs and 7 specialists). ITT analysis. Duration 6 months over winter
Participants	220 outpatients aged 40 to 80, with moderate or severe COPD defined by GOLD. 30% > FEV_1< 70%, with reversibility below 15%. All were smokers or ex-smokers. Mean age 62.3 years and 64% were male. Mean FEV_1 1.61 litres (54.7% predicted), Excluded were patients with severe medical conditions such as bronchial carcinoma, MI, alcoholism or heart failure Groups well-matched at baseline. Compliance said to be 'good' in all patients
Interventions	Cineole 2 x 100 mg, tds (total 600 mg) or placebo
Outcomes	Primary outcome: exacerbations - number, severity, duration Secondary outcomes: lung function, dyspnoea, quality of life (SGRQ), adverse effects Primary outcomes, dyspnoea and adverse effects assessed at each visit. Lung function assessed at 0, 3 and 6 months. Quality of life assessed at 0 and 6 months
Notes	German Jadad score 2

Risk of bias

Bias	Authors' judgement	Support for judgement

Worth 2009 (*Continued*)

Allocation concealment (selection bias)	High risk	Study said to be randomised, DB. Apart from an indication of stratification by site, there were no details given on the randomisation methods or blinding. Patients were instructed to take medication half an hour before meals to avoid the smell of cineole. No details on dropouts

Zheng 2008

Methods	Randomised, DB, PC, parallel, multicentre (22 centres). Duration 1 year. ITT analysis
Participants	709 outpatients with stable COPD defined by GOLD criteria with post-bronchodilator FEV_1/FVC ratio < 0.7, and FEV_1 between 25% and 79% predicted. Patients between ages of 40 and 80, with history of at least 2 COPD exacerbations in previous 2 years. Clinically stable in past 4 weeks. There were 91 dropouts (48 in mucolytic group and 43 in placebo group). Mean age 65 years, 78% male, mean FEV_1 1.09 litres (44.5% predicted). 75% had ever smoked. 49% were GOLD II, 39% GOLD III and 12% GOLD IV. Mean SGRQ was 42. Excluded were patients with asthma, non COPD respiratory disorders, LVRS or transplant, other conditions that would interfere with the study, on LTOT, or pulmonary rehabilitation, on oral corticosteroids, pregnancy or lactating. Patients in another investigational drug trial in past 12 weeks were also excluded 18% of intervention group and 15% of placebo group were on inhaled steroids
Interventions	Carbocysteine 1500 mg daily (2 x 250 mg tds) orally or placebo
Outcomes	Primary endpoint was exacerbation rate (defined by Anthonisen). Secondary endpoints covariance-adjusted exacerbation rate, quality of life, lung function and arterial oxygen saturation
Notes	Jadad score 5 Chinese, main PEACE study. The Lancet report for the main PEACE study involves 709 patients from 22 centres in China. There are another 2 references to the PEACE study from Japan (Tatsumi 2007a; Tatsumi 2007b). These both refer to the same sample of 142 patients - 70 in control group and 72 in the study group. Have written to Dr Zhong to ask if a sub-study or not of main PEACE study - was a different study

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	"Neither the investigator nor the patient knew the group allocation"

ATS: American Thoracic Society; bd: twice daily; BTS: British Thoracic Society; CF: cystic fibrosis; COPD: chronic obstructive pulmonary disease; CRQ: Chronic Respiratory Questionnaire; CXR: chest X-ray; DB: double-blind; ERS: European Respiratory

Society; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; GI: gastrointestinal; GOLD: Global Initiative for Obstructive Lung Disease; ICS: inhaled corticosteroids; ITT: intention-to-treat; LTOT: long-term oxygen therapy; LVRS: lung volume reduction surgery; MI: myocardial infarction; MRC: Medical Research Council; NAC: N-acetylcysteine; NYHA: New York Heart Association; od: once daily; OT: on treatment; PC: placebo-controlled; PEFR: peak expiratory flow rate; PP: per protocol; SCMC-Lys: carbocysteine lysine salt monohydrate; SD: standard deviation; SE: standard error; SGRQ: St George's Respiratory Questionnaire; tds: three times daily; VC: vital capacity; WHO: World Health Organization

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Baglioni 2001	Preliminary, small, open RCT NAC vs placebo in patients on LTOT, published in abstract form only, no numerical data on clinical outcomes
Cattaneo 2001	Only 20 days long
Christensen 1971	No response to 2 letters requesting more data. Old study - unlikely to be successful with further attempts. Did not evaluate primary outcome although did evaluate days sick
Edwards 1976	Did not evaluate primary outcome
Habich 1994	Included both asthmatics and COPD patients
Kasielski 2001	Did not evaluate clinical outcomes
Lukas 2005	Did not evaluate primary outcome
Maesen 1980	Did not evaluate primary outcome
Michnar 1996	Did not evaluate primary outcome
Rubin 1996	Did not evaluate primary outcome
Tatsumi 2007a	Even though randomised, not placebo-controlled or double-blind
Tatsumi 2007b	Even though randomised, not placebo-controlled or double-blind
Velazquez 2001	Only 4 weeks long
Wilhelmi 2010	Evaluated primary outcome, but although gave P values for a significant reduction in exacerbations in cineole group compared with placebo, no data were supplied for event rates

COPD: chronic obstructive pulmonary disease
LTOT: long-term oxygen therapy
NAC: N-acetylcysteine
RCT: randomised controlled trial
vs: versus

DATA AND ANALYSES

Comparison 1. Mucolytic versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Patients with no exacerbations in study period	22	4886	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.84 [1.63, 2.07]
1.1 Double-blind	22	4886	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.84 [1.63, 2.07]
1.2 Single-blind/open	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Patients with no exacerbation by decade	22	4886	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.84 [1.63, 2.07]
2.1 Before 1990	12	2304	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.34 [1.97, 2.79]
2.2 1990 to 2000	5	1105	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.91 [1.50, 2.44]
2.3 2000 onwards	5	1477	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.24 [1.01, 1.54]
3 Number of exacerbations per patient per month	26	6080	Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.04, -0.03]
3.1 Double-blind	25	6011	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.04, -0.03]
3.2 Single-blind/open	1	69	Mean Difference (IV, Fixed, 95% CI)	-0.13 [-0.22, -0.04]
4 Patients with no exacerbations in study period	24	5149	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.88 [1.68, 2.11]
4.1 Double-blind	22	4886	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.84 [1.63, 2.07]
4.2 Single-blind/open	2	263	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.91 [1.76, 4.83]
5 Patients with no exacerbations in the study period- winter treatment only	21	4007	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.20 [1.93, 2.51]
5.1 Double-blind	20	3844	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.18 [1.91, 2.49]
5.2 Single-blind/open	1	163	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.85 [1.49, 5.46]
6 Number of exacerbations for patient per month, by type or dose of mucolytic	26		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 N-acetylcysteine	14	3082	Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.05, -0.03]
6.2 N-acetylcysteine 400 mg daily	3	717	Mean Difference (IV, Fixed, 95% CI)	-0.18 [-0.21, -0.14]
6.3 N-acetylcysteine 600 mg daily	10	2236	Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.03, -0.01]
6.4 Other mucolytic	8	1752	Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.06, -0.03]
6.5 Carbocysteine	4	1340	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.04, -0.02]
7 Number of exacerbations, by FEV1	16	4447	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.04, -0.02]
7.1 Studies with mean FEV1 <= 50% predicted	2	362	Mean Difference (IV, Fixed, 95% CI)	-0.13 [-0.20, -0.05]
7.2 Studies with mean FEV1 > 50% predicted	14	4085	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.04, -0.02]
8 Number of exacerbations per COPD patient per year, no ICS	3	581	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.01, 0.04]

8.1 Not taking inhaled corticosteroids	3	581	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.01, 0.04]
9 Number of exacerbations, by study duration	26	6174	Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.04, -0.03]
9.1 Duration =< 3 months	5	918	Mean Difference (IV, Fixed, 95% CI)	-0.13 [-0.17, -0.09]
9.2 Duration > 3 months	21	5256	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.04, -0.02]
10 Number of exacerbations, by country	26	6174	Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.04, -0.03]
10.1 Italian	12	2556	Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.07, -0.05]
10.2 Non Italian	14	3618	Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.03, -0.02]
11 Number of exacerbations, in patients included for history of exacerbation	18	4260	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.04, -0.02]
12 Days of disability per patient per month	12	2305	Mean Difference (IV, Fixed, 95% CI)	-0.48 [-0.65, -0.30]
13 Days on antibiotics per patient per month	3	714	Mean Difference (IV, Fixed, 95% CI)	-0.53 [-0.76, -0.31]
14 Health-related quality of life (St George's Respiratory Questionnaire	3	1147	Mean Difference (IV, Random, 95% CI)	-3.62 [-8.04, 0.81]
15 Hospitalisation in the study period	2	678	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.70 [0.49, 1.01]
16 FEV1 or % predicted FEV1 or PEFR at end of study	15	2788	Std. Mean Difference (IV, Fixed, 95% CI)	0.12 [0.03, 0.21]
16.1 Double-blind	13	2525	Std. Mean Difference (IV, Fixed, 95% CI)	0.10 [0.01, 0.19]
16.2 Single-blind	2	263	Std. Mean Difference (IV, Fixed, 95% CI)	0.24 [-0.01, 0.48]
17 FVC at end of study	8	1490	Mean Difference (IV, Fixed, 95% CI)	0.06 [-0.04, 0.16]
18 Adverse effects	18	5176	Odds Ratio (M-H, Fixed, 95% CI)	0.82 [0.71, 0.95]
19 Death during study period	6	1821	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.75 [0.35, 1.64]

Comparison 2. Systemic thiol donor versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of exacerbations per patient per month	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Patients with no exacerbations in the study period	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
3 Days of disability per patient per month	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4 Adverse effects	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Mucolytic versus placebo, Outcome 1 Patients with no exacerbations in study period.

Review: Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease

Comparison: 1 Mucolytic versus placebo

Outcome: 1 Patients with no exacerbations in study period

Study or subgroup	Mucolytic n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Double-blind					
Grassi 1976	18/35	11/34		1.5 %	2.16 [0.84, 5.59]
Babolini 1980	134/254	58/241		10.5 %	3.34 [2.33, 4.79]
Borgia 1981	7/10	4/9		0.4 %	2.70 [0.46, 15.93]
Boman 1983	46/98	29/105		4.2 %	2.28 [1.29, 4.03]
Jackson 1984	41/61	36/60		2.5 %	1.36 [0.65, 2.85]
Grillage 1985	35/54	29/55		2.4 %	1.64 [0.77, 3.50]
McGavin 1985	11/72	8/76		1.5 %	1.52 [0.58, 3.98]
Meister 1986	37/90	34/91		3.9 %	1.17 [0.64, 2.12]
Cremonini 1986	8/21	0/20		0.6 %	10.66 [2.32, 49.05]
Castiglioni 1986	240/311	179/302		11.9 %	2.28 [1.63, 3.21]
Olivieri 1987	56/110	21/104		4.4 %	3.77 [2.16, 6.58]
Rasmussen 1988	28/44	24/47		2.0 %	1.66 [0.73, 3.80]
Grassi 1994	25/42	14/41		1.9 %	2.74 [1.16, 6.45]
Hansen 1994	36/59	34/70		2.9 %	1.64 [0.82, 3.29]
Allegra 1996	111/171	89/181		7.7 %	1.90 [1.24, 2.89]
Meister 1999	79/122	56/124		5.5 %	2.20 [1.33, 3.63]
Nowak 1999	114/147	101/148		5.2 %	1.60 [0.96, 2.67]
Moretti 2004	26/63	13/61		2.4 %	2.50 [1.18, 5.33]
Malerba 2004	64/115	63/119		5.2 %	1.11 [0.67, 1.86]
Zheng 2008	159/353	151/354		15.6 %	1.10 [0.82, 1.48]
Schermer 2009	22/96	27/96		3.3 %	0.76 [0.40, 1.45]
Worth 2009	79/110	60/110		4.6 %	2.09 [1.21, 3.62]
Subtotal (95% CI)	**2438**	**2448**	◆	**100.0 %**	**1.84 [1.63, 2.07]**
Total events: 1376 (Mucolytic), 1041 (Placebo)					

0.05 0.2 1 5 20

Favours placebo Favours mucolytic

(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Mucolytic n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Heterogeneity: Chi² = 52.31, df = 21 (P = 0.00017); I² =60%					
Test for overall effect: Z = 10.18 (P < 0.00001)					
2 Single-blind/open					
Subtotal (95% CI)	**0**	**0**		**0.0 %**	**0.0 [0.0, 0.0]**
Total events: 0 (Mucolytic), 0 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	**2438**	**2448**	♦	**100.0 %**	**1.84 [1.63, 2.07]**
Total events: 1376 (Mucolytic), 1041 (Placebo)					
Heterogeneity: Chi² = 52.31, df = 21 (P = 0.00017); I² =60%					
Test for overall effect: Z = 10.18 (P < 0.00001)					
Test for subgroup differences: Not applicable					

Analysis 1.2. Comparison 1 Mucolytic versus placebo, Outcome 2 Patients with no exacerbation by decade.

Review: Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease

Comparison: 1 Mucolytic versus placebo

Outcome: 2 Patients with no exacerbation by decade

Study or subgroup	Mucolytic n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Before 1990					
Grassi 1976	18/35	11/34		1.5 %	2.16 [0.84, 5.59]
Babolini 1980	134/254	58/241		10.5 %	3.34 [2.33, 4.79]
Borgia 1981	7/10	4/9		0.4 %	2.70 [0.46, 15.93]
Boman 1983	46/98	29/105		4.2 %	2.28 [1.29, 4.03]
Jackson 1984	41/61	36/60		2.5 %	1.36 [0.65, 2.85]
Grillage 1985	35/54	29/55		2.4 %	1.64 [0.77, 3.50]
McGavin 1985	11/72	8/76		1.5 %	1.52 [0.58, 3.98]
Meister 1986	37/90	34/91		3.9 %	1.17 [0.64, 2.12]
Castiglioni 1986	240/311	179/302		11.9 %	2.28 [1.63, 3.21]
Cremonini 1986	8/21	0/20		0.6 %	10.66 [2.32, 49.05]
Olivieri 1987	56/110	21/104		4.4 %	3.77 [2.16, 6.58]
Rasmussen 1988	28/44	24/47		2.0 %	1.66 [0.73, 3.80]
Subtotal (95% CI)	**1160**	**1144**		**45.8 %**	**2.34 [1.97, 2.79]**
Total events: 661 (Mucolytic), 433 (Placebo)					
Heterogeneity: Chi^2 = 19.97, df = 11 (P = 0.05); I^2 =45%					
Test for overall effect: Z = 9.65 (P < 0.00001)					
2 1990 to 2000					
Hansen 1994	36/59	34/70		2.9 %	1.64 [0.82, 3.29]
Grassi 1994	25/42	14/41		1.9 %	2.74 [1.16, 6.45]
Allegra 1996	111/171	89/181		7.7 %	1.90 [1.24, 2.89]
Meister 1999	79/122	56/124		5.5 %	2.20 [1.33, 3.63]
Nowak 1999	114/147	101/148		5.2 %	1.60 [0.96, 2.67]
Subtotal (95% CI)	**541**	**564**		**23.1 %**	**1.91 [1.50, 2.44]**
Total events: 365 (Mucolytic), 294 (Placebo)					
Heterogeneity: Chi^2 = 1.62, df = 4 (P = 0.80); I^2 =0.0%					
Test for overall effect: Z = 5.22 (P < 0.00001)					
3 2000 onwards					

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Study or subgroup	Mucolytic n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Malerba 2004	64/115	63/119		5.2 %	1.11 [0.67, 1.86]
Moretti 2004	26/63	13/61		2.4 %	2.50 [1.18, 5.33]
Zheng 2008	159/353	151/354		15.6 %	1.10 [0.82, 1.48]
Worth 2009	79/110	60/110		4.6 %	2.09 [1.21, 3.62]
Schermer 2009	22/96	27/96		3.3 %	0.76 [0.40, 1.45]
Subtotal (95% CI)	**737**	**740**		**31.0 %**	**1.24 [1.01, 1.54]**
Total events: 350 (Mucolytic), 314 (Placebo)					
Heterogeneity: Chi^2 = 9.82, df = 4 (P = 0.04); I^2 =59%					
Test for overall effect: Z = 2.04 (P = 0.042)					
Total (95% CI)	**2438**	**2448**		**100.0 %**	**1.84 [1.63, 2.07]**
Total events: 1376 (Mucolytic), 1041 (Placebo)					
Heterogeneity: Chi^2 = 52.31, df = 21 (P = 0.00017); I^2 =60%					
Test for overall effect: Z = 10.18 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 20.91, df = 2 (P = 0.00), I^2 =90%					

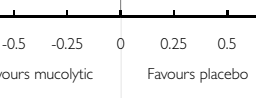
Analysis 1.3. Comparison 1 Mucolytic versus placebo, Outcome 3 Number of exacerbations per patient per month.

Review: Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease

Comparison: 1 Mucolytic versus placebo

Outcome: 3 Number of exacerbations per patient per month

Study or subgroup	Mucolytic N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Double-blind						
Grassi 1976	35	0.14 (0.15)	34	0.27 (0.21)		-0.13 [-0.22, -0.04]
Babolini 1980	254	0.13 (0.18)	241	0.33 (0.27)		-0.20 [-0.24, -0.16]
Borgia 1981	10	0.05 (0.08)	9	0.15 (0.17)		-0.10 [-0.22, 0.02]
Boman 1983	98	0.2 (0.27)	105	0.32 (0.3)		-0.12 [-0.20, -0.04]
Jackson 1984	61	0.11 (0)	60	0.13 (0)		0.0 [0.0, 0.0]
Grillage 1985	54	0.1 (0)	55	0.12 (0)		0.0 [0.0, 0.0]
McGavin 1985	72	0.42 (0.34)	76	0.52 (0.35)		-0.10 [-0.21, 0.01]
Meister 1986	90	0.15 (0.15)	91	0.2 (0.19)		-0.05 [-0.10, 0.00]
Cremonini 1986	21	0.25 (0.23)	20	0.71 (0.29)		-0.46 [-0.62, -0.30]
Castiglioni 1986	311	0.1 (0.21)	302	0.2 (0.29)		-0.10 [-0.14, -0.06]
Olivieri 1987	110	0.18 (0.31)	104	0.33 (0.41)		-0.15 [-0.25, -0.05]
Parr 1987	243	0.18 (0.21)	210	0.21 (0.21)		-0.03 [-0.07, 0.01]
Rasmussen 1988	44	0.13 (0.21)	47	0.14 (0.19)		-0.01 [-0.09, 0.07]
Bontognali 1991	30	0.7 (3.76)	30	1.27 (4.58)		-0.57 [-2.69, 1.55]
Grassi 1994	42	0.16 (0.29)	41	0.45 (0.43)		-0.29 [-0.45, -0.13]
Hansen 1994	59	0.11 (0.15)	70	0.16 (0.19)		-0.05 [-0.11, 0.01]
Allegra 1996	223	0.07 (0.11)	218	0.11 (0.14)		-0.04 [-0.06, -0.02]
Nowak 1999	147	0.03 (0.06)	148	0.06 (0.12)		-0.03 [-0.05, -0.01]
Meister 1999	122	0.06 (0.15)	124	0.1 (0.15)		-0.04 [-0.08, 0.00]
Malerba 2004	115	0.06 (0.08)	119	0.07 (0.08)		-0.01 [-0.03, 0.01]
Moretti 2004	63	0.12 (0.14)	61	0.17 (0.17)		-0.05 [-0.10, 0.00]
Decramer 2005	256	0.1 (0.11)	267	0.11 (0.16)		-0.01 [-0.03, 0.01]
Zheng 2008	353	0.08416 (0.094)	354	0.11 (0.094)		-0.03 [-0.04, -0.01]
Worth 2009	110	0.067 (0.136)	110	0.15 (0.24)		-0.08 [-0.13, -0.03]



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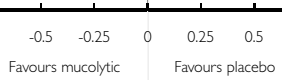
Study or subgroup	Mucolytic N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Schermer 2009	96	0.08 (0.1)	96	0.06 (0.05)		0.02 [0.00, 0.04]
Subtotal (95% CI)	**3019**		**2992**			**-0.03 [-0.04, -0.03]**
Heterogeneity: Chi^2 = 166.61, df = 22 (P<0.00001); I^2 =87%						
Test for overall effect: Z = 9.65 (P < 0.00001)						
2 Single-blind/open						
Pela 1999	35	0.14 (0.15)	34	0.27 (0.21)		-0.13 [-0.22, -0.04]
Subtotal (95% CI)	**35**		**34**			**-0.13 [-0.22, -0.04]**
Heterogeneity: not applicable						
Test for overall effect: Z = 2.95 (P = 0.0032)						
Total (95% CI)	**3054**		**3026**			**-0.04 [-0.04, -0.03]**
Heterogeneity: Chi^2 = 171.26, df = 23 (P<0.00001); I^2 =87%						
Test for overall effect: Z = 9.86 (P < 0.00001)						
Test for subgroup differences: Chi^2 = 4.65, df = 1 (P = 0.03), I^2 =78%						



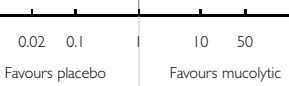
Analysis 1.4. Comparison 1 Mucolytic versus placebo, Outcome 4 Patients with no exacerbations in study period.

Review: Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease

Comparison: 1 Mucolytic versus placebo

Outcome: 4 Patients with no exacerbations in study period

Study or subgroup	Mucolytic n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Double-blind					
Grassi 1976	18/35	11/34		1.4 %	2.16 [0.84, 5.59]
Babolini 1980	134/254	58/241		10.0 %	3.34 [2.33, 4.79]
Borgia 1981	7/10	4/9		0.4 %	2.70 [0.46, 15.93]
Boman 1983	46/98	29/105		4.0 %	2.28 [1.29, 4.03]
Jackson 1984	41/61	36/60		2.4 %	1.36 [0.65, 2.85]
Grillage 1985	35/54	29/55		2.3 %	1.64 [0.77, 3.50]
McGavin 1985	11/72	8/76		1.4 %	1.52 [0.58, 3.98]
Meister 1986	37/90	34/91		3.7 %	1.17 [0.64, 2.12]
Castiglioni 1986	240/311	179/302		11.3 %	2.28 [1.63, 3.21]
Cremonini 1986	8/21	0/20		0.6 %	10.66 [2.32, 49.05]
Olivieri 1987	56/110	21/104		4.2 %	3.77 [2.16, 6.58]
Rasmussen 1988	28/44	24/47		1.9 %	1.66 [0.73, 3.80]
Hansen 1994	36/59	34/70		2.7 %	1.64 [0.82, 3.29]
Grassi 1994	25/42	14/41		1.8 %	2.74 [1.16, 6.45]
Allegra 1996	111/171	89/181		7.3 %	1.90 [1.24, 2.89]
Meister 1999	79/122	56/124		5.2 %	2.20 [1.33, 3.63]
Nowak 1999	114/147	101/148		5.0 %	1.60 [0.96, 2.67]
Malerba 2004	64/115	63/119		4.9 %	1.11 [0.67, 1.86]
Moretti 2004	26/63	13/61		2.3 %	2.50 [1.18, 5.33]
Zheng 2008	159/353	151/354		14.8 %	1.10 [0.82, 1.48]
Worth 2009	79/110	60/110		4.4 %	2.09 [1.21, 3.62]
Schermer 2009	22/96	27/96		3.1 %	0.76 [0.40, 1.45]
Subtotal (95% CI)	**2438**	**2448**		**94.9 %**	**1.84 [1.63, 2.07]**
Total events: 1376 (Mucolytic), 1041 (Placebo)					



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Study or subgroup	Mucolytic n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Heterogeneity: Chi² = 52.31, df = 21 (P = 0.00017); I² =60%					
Test for overall effect: Z = 10.18 (P < 0.00001)					
2 Single-blind/open					
Pela 1999	37/83	17/80		3.1 %	2.85 [1.49, 5.46]
Bachh 2007	25/50	12/50		2.0 %	3.02 [1.35, 6.77]
Subtotal (95% CI)	**133**	**130**		**5.1 %**	**2.91 [1.76, 4.83]**
Total events: 62 (Mucolytic), 29 (Placebo)					
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.91); I² =0.0%					
Test for overall effect: Z = 4.14 (P = 0.000035)					
Total (95% CI)	**2571**	**2578**		**100.0 %**	**1.88 [1.68, 2.11]**
Total events: 1438 (Mucolytic), 1070 (Placebo)					
Heterogeneity: Chi² = 55.34, df = 23 (P = 0.00017); I² =58%					
Test for overall effect: Z = 10.85 (P < 0.00001)					
Test for subgroup differences: Chi² = 3.02, df = 1 (P = 0.08), I² =67%					

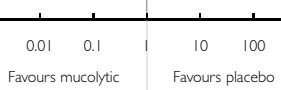
Analysis 1.5. Comparison 1 Mucolytic versus placebo, Outcome 5 Patients with no exacerbations in the study period- winter treatment only.

Review: Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease

Comparison: 1 Mucolytic versus placebo

Outcome: 5 Patients with no exacerbations in the study period- winter treatment only

Study or subgroup	Mucolytic n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Double-blind					
Allegra 1996	111/171	89/181		9.5 %	1.90 [1.24, 2.89]
Babolini 1980	134/254	58/241		12.9 %	3.34 [2.33, 4.79]
Boman 1983	46/98	29/105		5.2 %	2.28 [1.29, 4.03]
Borgia 1981	7/10	4/9		0.5 %	2.70 [0.46, 15.93]
Castiglioni 1986	240/311	179/302		14.6 %	2.28 [1.63, 3.21]
Cremonini 1986	8/21	0/20		0.7 %	10.66 [2.32, 49.05]
Grassi 1976	18/35	11/34		1.9 %	2.16 [0.84, 5.59]
Grassi 1994	25/42	14/41		2.3 %	2.74 [1.16, 6.45]
Grillage 1985	35/54	29/55		2.9 %	1.64 [0.77, 3.50]
Hansen 1994	36/59	34/70		3.5 %	1.64 [0.82, 3.29]
Jackson 1984	41/61	36/60		3.1 %	1.36 [0.65, 2.85]
Malerba 2004	28/44	24/47		2.5 %	1.66 [0.73, 3.80]
McGavin 1985	11/72	8/76		1.8 %	1.52 [0.58, 3.98]
Meister 1986	37/90	34/91		4.8 %	1.17 [0.64, 2.12]
Meister 1999	79/122	56/124		6.7 %	2.20 [1.33, 3.63]
Moretti 2004	26/63	13/61		3.0 %	2.50 [1.18, 5.33]
Nowak 1999	114/147	101/148		6.4 %	1.60 [0.96, 2.67]
Olivieri 1987	56/110	21/104		5.4 %	3.77 [2.16, 6.58]
Rasmussen 1988	28/44	24/47		2.5 %	1.66 [0.73, 3.80]
Worth 2009	79/110	60/110		5.7 %	2.09 [1.21, 3.62]
Subtotal (95% CI)	**1918**	**1926**		**96.0 %**	**2.18 [1.91, 2.49]**
Total events: 1159 (Mucolytic), 824 (Placebo)					
Heterogeneity: Chi^2 = 23.93, df = 19 (P = 0.20); I^2 =21%					
Test for overall effect: Z = 11.49 (P < 0.00001)					
2 Single-blind/open					



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Study or subgroup	Mucolytic n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Pela 1999	37/83	17/80		4.0 %	2.85 [1.49, 5.46]
Subtotal (95% CI)	**83**	**80**		**4.0 %**	**2.85 [1.49, 5.46]**
Total events: 37 (Mucolytic), 17 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.15 (P = 0.0016)					
Total (95% CI)	**2001**	**2006**		**100.0 %**	**2.20 [1.93, 2.51]**
Total events: 1196 (Mucolytic), 841 (Placebo)					
Heterogeneity: Chi^2 = 24.56, df = 20 (P = 0.22); I^2 =19%					
Test for overall effect: Z = 11.89 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 0.63, df = 1 (P = 0.43), I^2 =0.0%					

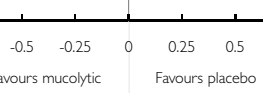
Analysis 1.6. Comparison 1 Mucolytic versus placebo, Outcome 6 Number of exacerbations for patient per month, by type or dose of mucolytic.

Review: Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease

Comparison: 1 Mucolytic versus placebo

Outcome: 6 Number of exacerbations for patient per month, by type or dose of mucolytic

Study or subgroup	Mucolytic N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 N-acetylcysteine						
Babolini 1980	254	0.13 (0.18)	241	0.33 (0.27)		-0.20 [-0.24, -0.16]
Boman 1983	98	0.2 (0.27)	105	0.32 (0.3)		-0.12 [-0.20, -0.04]
Borgia 1981	10	0.05 (0.08)	9	0.15 (0.17)		-0.10 [-0.22, 0.02]
Decramer 2005	256	0.1 (0.11)	267	0.11 (0.16)		-0.01 [-0.03, 0.01]
Grassi 1976	35	0.14 (0.15)	34	0.27 (0.21)		-0.13 [-0.22, -0.04]
Hansen 1994	59	0.11 (0.15)	70	0.16 (0.19)		-0.05 [-0.11, 0.01]
Jackson 1984	61	0.11 (0)	60	0.13 (0)		0.0 [0.0, 0.0]
McGavin 1985	72	0.42 (0.34)	76	0.52 (0.35)		-0.10 [-0.21, 0.01]
Meister 1986	90	0.15 (0.15)	91	0.2 (0.19)		-0.05 [-0.10, 0.00]
Nowak 1999	147	0.03 (0.06)	148	0.06 (0.12)		-0.03 [-0.05, -0.01]
Parr 1987	243	0.18 (0.21)	210	0.21 (0.21)		-0.03 [-0.07, 0.01]
Pela 1999	83	0.17 (0.18)	80	0.29 (0.32)		-0.12 [-0.20, -0.04]
Rasmussen 1988	44	0.13 (0.21)	47	0.14 (0.19)		-0.01 [-0.09, 0.07]
Schermer 2009	96	0.08 (0.14)	96	0.06 (0.09)		0.02 [-0.01, 0.05]
Subtotal (95% CI)	**1548**		**1534**			**-0.04 [-0.05, -0.03]**
Heterogeneity: Chi² = 94.16, df = 12 (P<0.00001); I² =87%						
Test for overall effect: Z = 7.03 (P < 0.00001)						
2 N-acetylcysteine 400 mg daily						
Babolini 1980	254	0.13 (0.18)	241	0.33 (0.27)		-0.20 [-0.24, -0.16]
Boman 1983	98	0.2 (0.27)	105	0.32 (0.3)		-0.12 [-0.20, -0.04]
Borgia 1981	10	0.05 (0.08)	9	0.15 (0.17)		-0.10 [-0.22, 0.02]
Subtotal (95% CI)	**362**		**355**			**-0.18 [-0.21, -0.14]**
Heterogeneity: Chi² = 4.80, df = 2 (P = 0.09); I² =58%						
Test for overall effect: Z = 9.99 (P < 0.00001)						
3 N-acetylcysteine 600 mg daily						
Decramer 2005	256	0.1 (0.11)	267	0.11 (0.16)		-0.01 [-0.03, 0.01]



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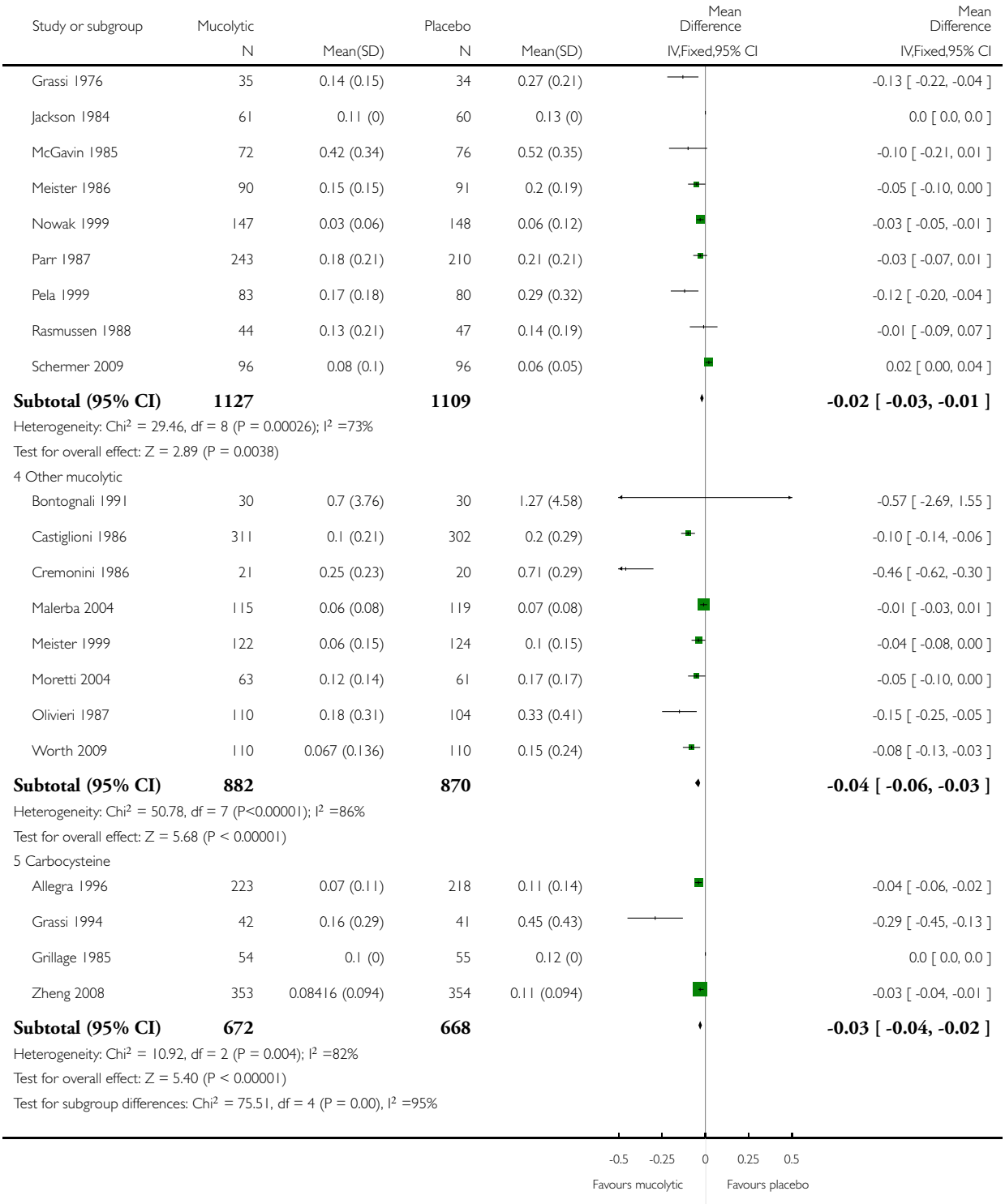


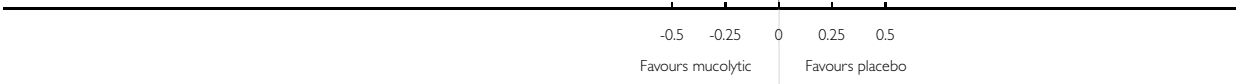
Analysis 1.7. Comparison 1 Mucolytic versus placebo, Outcome 7 Number of exacerbations, by FEV1.

Review: Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease

Comparison: 1 Mucolytic versus placebo

Outcome: 7 Number of exacerbations, by FEV1

Study or subgroup	Mucolytic N	Mucolytic Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Studies with mean FEV1 <= 50% predicted							
McGavin 1985	72	0.42 (0.34)	76	0.52 (0.35)		0.5 %	-0.10 [-0.21, 0.01]
Olivieri 1987	110	0.18 (0.31)	104	0.33 (0.41)		0.6 %	-0.15 [-0.25, -0.05]
Subtotal (95% CI)	**182**		**180**			**1.0 %**	**-0.13 [-0.20, -0.05]**
Heterogeneity: Chi² = 0.44, df = 1 (P = 0.51); I² =0.0%							
Test for overall effect: Z = 3.42 (P = 0.00062)							
2 Studies with mean FEV1 > 50% predicted							
Allegra 1996	223	0.07 (0.11)	218	0.11 (0.14)		10.0 %	-0.04 [-0.06, -0.02]
Boman 1983	98	0.2 (0.27)	105	0.32 (0.3)		0.9 %	-0.12 [-0.20, -0.04]
Castiglioni 1986	311	0.1 (0.21)	302	0.2 (0.29)		3.4 %	-0.10 [-0.14, -0.06]
Cremonini 1986	21	0.25 (0.23)	20	0.71 (0.29)		0.2 %	-0.46 [-0.62, -0.30]
Decramer 2005	256	0.1 (0.11)	267	0.11 (0.16)		10.1 %	-0.01 [-0.03, 0.01]
Grassi 1994	42	0.16 (0.29)	41	0.45 (0.43)		0.2 %	-0.29 [-0.45, -0.13]
Malerba 2004	115	0.06 (0.08)	119	0.07 (0.08)		13.2 %	-0.01 [-0.03, 0.01]
Meister 1999	122	0.06 (0.15)	124	0.1 (0.15)		4.0 %	-0.04 [-0.08, 0.00]
Moretti 2004	63	0.12 (0.14)	61	0.17 (0.17)		1.8 %	-0.05 [-0.10, 0.00]
Nowak 1999	147	0.03 (0.06)	148	0.06 (0.12)		11.9 %	-0.03 [-0.05, -0.01]
Pela 1999	83	0.17 (0.18)	80	0.29 (0.32)		0.9 %	-0.12 [-0.20, -0.04]
Schermer 2009	96	0.08 (0.1)	96	0.06 (0.05)		11.1 %	0.02 [0.00, 0.04]
Worth 2009	110	0.067 (0.136)	110	0.15 (0.24)		2.1 %	-0.08 [-0.13, -0.03]
Zheng 2008	353	0.08416 (0.094)	354	0.11 (0.094)		29.0 %	-0.03 [-0.04, -0.01]
Subtotal (95% CI)	**2040**		**2045**			**99.0 %**	**-0.03 [-0.04, -0.02]**
Heterogeneity: Chi² = 90.31, df = 13 (P<0.00001); I² =86%							
Test for overall effect: Z = 7.23 (P < 0.00001)							
Total (95% CI)	**2222**		**2225**			**100.0 %**	**-0.03 [-0.04, -0.02]**
Heterogeneity: Chi² = 97.88, df = 15 (P<0.00001); I² =85%							
Test for overall effect: Z = 7.54 (P < 0.00001)							
Test for subgroup differences: Chi² = 7.13, df = 1 (P = 0.01), I² =86%							



Analysis 1.8. Comparison 1 Mucolytic versus placebo, Outcome 8 Number of exacerbations per COPD patient per year, no ICS.

Review: Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease

Comparison: 1 Mucolytic versus placebo

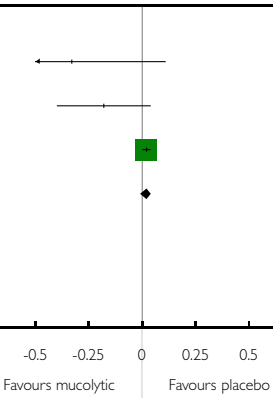
Outcome: 8 Number of exacerbations per COPD patient per year, no ICS

Study or subgroup	Mucolytic N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Not taking inhaled corticosteroids							
Decramer 2005	77	0.96 (1.36)	78	1.29 (1.46)		0.3 %	-0.33 [-0.77, 0.11]
Malerba 2004	115	0.69 (0.87)	119	0.87 (0.88)		1.0 %	-0.18 [-0.40, 0.04]
Schermer 2009	96	0.08 (0.1)	96	0.06 (0.05)		98.8 %	0.02 [0.00, 0.04]
Total (95% CI)	**288**		**293**			**100.0 %**	**0.02 [-0.01, 0.04]**

Heterogeneity: $Chi^2 = 5.38$, df = 2 (P = 0.07); $I^2 = 63\%$

Test for overall effect: Z = 1.51 (P = 0.13)

Test for subgroup differences: Not applicable



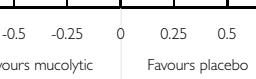
Analysis 1.9. Comparison 1 Mucolytic versus placebo, Outcome 9 Number of exacerbations, by study duration.

Review: Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease

Comparison: 1 Mucolytic versus placebo

Outcome: 9 Number of exacerbations, by study duration

Study or subgroup	Mucolytic N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Duration =< 3 months						
Bontognali 1991	30	0.7 (3.76)	30	1.27 (4.58)		-0.57 [-2.69, 1.55]
Castiglioni 1986	311	0.1 (0.21)	302	0.2 (0.29)		-0.10 [-0.14, -0.06]
Cremonini 1986	21	0.25 (0.23)	20	0.71 (0.29)		-0.46 [-0.62, -0.30]
Grassi 1994	42	0.16 (0.29)	41	0.45 (0.43)		-0.29 [-0.45, -0.13]
Jackson 1984	61	0.11 (0)	60	0.13 (0)		0.0 [0.0, 0.0]
Subtotal (95% CI)	**465**		**453**			**-0.13 [-0.17, -0.09]**
Heterogeneity: Chi^2 = 22.43, df = 3 (P = 0.00005); I^2 =87%						
Test for overall effect: Z = 6.78 (P < 0.00001)						
2 Duration > 3 months						
Grillage 1985	54	0.1 (0)	55	0.12 (0)		0.0 [0.0, 0.0]
Allegra 1996	223	0.07 (0.11)	218	0.11 (0.14)		-0.04 [-0.06, -0.02]
Babolini 1980	254	0.13 (0.18)	241	0.33 (0.27)		-0.20 [-0.24, -0.16]
Boman 1983	98	0.2 (0.27)	105	0.32 (0.3)		-0.12 [-0.20, -0.04]
Borgia 1981	10	0.05 (0.08)	9	0.15 (0.17)		-0.10 [-0.22, 0.02]
Decramer 2005	256	0.1 (0.11)	267	0.11 (0.16)		-0.01 [-0.03, 0.01]
Grassi 1976	35	0.14 (0.15)	34	0.27 (0.21)		-0.13 [-0.22, -0.04]
Hansen 1994	59	0.11 (0.15)	70	0.16 (0.19)		-0.05 [-0.11, 0.01]
Malerba 2004	115	0.06 (0.08)	119	0.07 (0.08)		-0.01 [-0.03, 0.01]
McGavin 1985	72	0.42 (0.34)	76	0.52 (0.35)		-0.10 [-0.21, 0.01]
Meister 1986	90	0.15 (0.15)	91	0.2 (0.19)		-0.05 [-0.10, 0.00]
Meister 1999	122	0.06 (0.15)	124	0.1 (0.15)		-0.04 [-0.08, 0.00]
Moretti 2004	63	0.12 (0.14)	61	0.17 (0.17)		-0.05 [-0.10, 0.00]
Nowak 1999	147	0.03 (0.06)	148	0.06 (0.12)		-0.03 [-0.05, -0.01]
Olivieri 1987	110	0.18 (0.31)	104	0.33 (0.41)		-0.15 [-0.25, -0.05]
Parr 1987	243	0.18 (0.21)	210	0.21 (0.21)		-0.03 [-0.07, 0.01]



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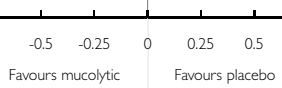
Study or subgroup	Mucolytic N	Mucolytic Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Pela 1999	83	0.17 (0.18)	80	0.29 (0.32)		-0.12 [-0.20, -0.04]
Rasmussen 1988	44	0.13 (0.21)	47	0.14 (0.19)		-0.01 [-0.09, 0.07]
Zheng 2008	353	0.08416 (0.094)	354	0.11 (0.094)		-0.03 [-0.04, -0.01]
Worth 2009	110	0.067 (0.136)	110	0.15 (0.24)		-0.08 [-0.13, -0.03]
Schermer 2009	96	0.08 (0.1)	96	0.06 (0.05)		0.02 [0.00, 0.04]
Subtotal (95% CI)	**2637**		**2619**			**-0.03 [-0.04, -0.02]**
Heterogeneity: Chi^2 = 123.09, df = 19 (P<0.00001); I^2 =85%						
Test for overall effect: Z = 8.76 (P < 0.00001)						
Total (95% CI)	**3102**		**3072**			**-0.04 [-0.04, -0.03]**
Heterogeneity: Chi^2 = 170.93, df = 23 (P<0.00001); I^2 =87%						
Test for overall effect: Z = 9.87 (P < 0.00001)						
Test for subgroup differences: Chi^2 = 25.41, df = 1 (P = 0.00), I^2 =96%						



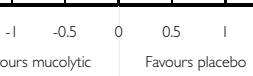
Analysis 1.10. Comparison 1 Mucolytic versus placebo, Outcome 10 Number of exacerbations, by country.

Review: Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease

Comparison: 1 Mucolytic versus placebo

Outcome: 10 Number of exacerbations, by country

Study or subgroup	Mucolytic N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Italian						
Allegra 1996	223	0.07 (0.11)	218	0.11 (0.14)		-0.04 [-0.06, -0.02]
Babolini 1980	254	0.13 (0.18)	241	0.33 (0.27)		-0.20 [-0.24, -0.16]
Bontognali 1991	30	0.7 (3.76)	30	1.27 (4.58)		-0.57 [-2.69, 1.55]
Borgia 1981	10	0.05 (0.08)	9	0.15 (0.17)		-0.10 [-0.22, 0.02]
Castiglioni 1986	311	0.1 (0.21)	302	0.2 (0.29)		-0.10 [-0.14, -0.06]
Cremonini 1986	21	0.25 (0.23)	20	0.71 (0.29)		-0.46 [-0.62, -0.30]
Grassi 1976	35	0.14 (0.15)	34	0.27 (0.21)		-0.13 [-0.22, -0.04]
Grassi 1994	42	0.16 (0.29)	41	0.45 (0.43)		-0.29 [-0.45, -0.13]
Malerba 2004	115	0.06 (0.08)	119	0.07 (0.08)		-0.01 [-0.03, 0.01]
Moretti 2004	63	0.12 (0.14)	61	0.17 (0.17)		-0.05 [-0.10, 0.00]
Olivieri 1987	110	0.18 (0.31)	104	0.33 (0.41)		-0.15 [-0.25, -0.05]
Pela 1999	83	0.17 (0.18)	80	0.29 (0.32)		-0.12 [-0.20, -0.04]
Subtotal (95% CI)	**1297**		**1259**			**-0.06 [-0.07, -0.05]**
Heterogeneity: Chi² = 115.59, df = 11 (P<0.00001); I² =90%						
Test for overall effect: Z = 9.49 (P < 0.00001)						
2 Non Italian						
Grillage 1985	54	0.1 (0)	55	0.12 (0)		0.0 [0.0, 0.0]
Meister 1999	122	0.06 (0.15)	124	0.1 (0.15)		-0.04 [-0.08, 0.00]
Boman 1983	98	0.2 (0.27)	105	0.32 (0.3)		-0.12 [-0.20, -0.04]
Decramer 2005	256	0.1 (0.11)	267	0.11 (0.16)		-0.01 [-0.03, 0.01]
Hansen 1994	59	0.11 (0.15)	70	0.16 (0.19)		-0.05 [-0.11, 0.01]
Jackson 1984	61	0.11 (0)	60	0.13 (0)		0.0 [0.0, 0.0]
McGavin 1985	72	0.42 (0.34)	76	0.52 (0.35)		-0.10 [-0.21, 0.01]
Meister 1986	90	0.15 (0.15)	91	0.2 (0.19)		-0.05 [-0.10, 0.00]
Nowak 1999	147	0.03 (0.06)	148	0.06 (0.12)		-0.03 [-0.05, -0.01]



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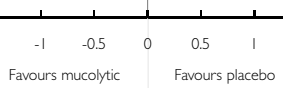
Study or subgroup	Mucolytic N	Mucolytic Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Parr 1987	243	0.18 (0.21)	210	0.21 (0.21)		-0.03 [-0.07, 0.01]
Rasmussen 1988	44	0.13 (0.21)	47	0.14 (0.19)		-0.01 [-0.09, 0.07]
Zheng 2008	353	0.08416 (0.094)	354	0.11 (0.094)		-0.03 [-0.04, -0.01]
Worth 2009	110	0.067 (0.136)	110	0.15 (0.24)		-0.08 [-0.13, -0.03]
Schermer 2009	96	0.08 (0.1)	96	0.06 (0.05)		0.02 [0.00, 0.04]
Subtotal (95% CI)	**1805**		**1813**			**-0.02 [-0.03, -0.02]**
Heterogeneity: Chi^2 = 32.19, df = 11 (P = 0.00071); I^2 =66%						
Test for overall effect: Z = 5.52 (P < 0.00001)						
Total (95% CI)	**3102**		**3072**			**-0.04 [-0.04, -0.03]**
Heterogeneity: Chi^2 = 170.93, df = 23 (P<0.00001); I^2 =87%						
Test for overall effect: Z = 9.87 (P < 0.00001)						
Test for subgroup differences: Chi^2 = 23.15, df = 1 (P = 0.00), I^2 =96%						



Analysis 1.11. Comparison 1 Mucolytic versus placebo, Outcome 11 Number of exacerbations, in patients included for history of exacerbation.

Review: Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease

Comparison: 1 Mucolytic versus placebo

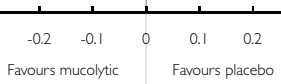
Outcome: 11 Number of exacerbations, in patients included for history of exacerbation

Study or subgroup	Mucolytic N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Allegra 1996	223	0.07 (0.11)	218	0.11 (0.14)		-0.04 [-0.06, -0.02]
Boman 1983	98	0.2 (0.27)	105	0.32 (0.3)		-0.12 [-0.20, -0.04]
Bontognali 1991	30	0.7 (3.76)	30	1.27 (4.58)		-0.57 [-2.69, 1.55]
Borgia 1981	10	0.05 (0.08)	9	0.15 (0.17)		-0.10 [-0.22, 0.02]
Decramer 2005	256	0.1 (0.11)	267	0.11 (0.16)		-0.01 [-0.03, 0.01]
Grassi 1994	42	0.16 (0.29)	41	0.45 (0.43)		-0.29 [-0.45, -0.13]
Grillage 1985	54	0.1 (0)	55	0.12 (0)		0.0 [0.0, 0.0]
Hansen 1994	59	0.11 (0.15)	70	0.16 (0.19)		-0.05 [-0.11, 0.01]
Malerba 2004	115	0.06 (0.08)	119	0.07 (0.08)		-0.01 [-0.03, 0.01]
McGavin 1985	72	0.42 (0.34)	76	0.52 (0.35)		-0.10 [-0.21, 0.01]
Meister 1986	90	0.15 (0.15)	91	0.2 (0.19)		-0.05 [-0.10, 0.00]
Meister 1999	122	0.06 (0.15)	124	0.1 (0.15)		-0.04 [-0.08, 0.00]
Moretti 2004	63	0.12 (0.14)	61	0.17 (0.17)		-0.05 [-0.10, 0.00]
Nowak 1999	147	0.03 (0.06)	148	0.06 (0.12)		-0.03 [-0.05, -0.01]
Olivieri 1987	110	0.18 (0.31)	104	0.33 (0.41)		-0.15 [-0.25, -0.05]
Parr 1987	243	0.18 (0.21)	210	0.21 (0.21)		-0.03 [-0.07, 0.01]
Rasmussen 1988	44	0.13 (0.21)	47	0.14 (0.19)		-0.01 [-0.09, 0.07]
Zheng 2008	353	0.08416 (0.094)	354	0.11 (0.094)		-0.03 [-0.04, -0.01]
Total (95% CI)	**2131**		**2129**		◆	**-0.03 [-0.04, -0.02]**

Heterogeneity: Chi^2 = 33.54, df = 16 (P = 0.01); I^2 =52%

Test for overall effect: Z = 7.49 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 1.12. Comparison 1 Mucolytic versus placebo, Outcome 12 Days of disability per patient per month.

Review: Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease

Comparison: 1 Mucolytic versus placebo

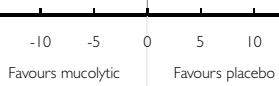
Outcome: 12 Days of disability per patient per month

Study or subgroup	Mucolytic N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Allegra 1996	171	0.63 (1.23)	181	1.12 (1.61)		-0.49 [-0.79, -0.19]
Bontognali 1991	30	4.6 (3.76)	30	7.87 (4.58)		-3.27 [-5.39, -1.15]
Cegla 1988	86	0.59 (0)	87	0.86 (0)		0.0 [0.0, 0.0]
Cremonini 1986	20	0.55 (0.75)	21	2.54 (2.25)		-1.99 [-3.01, -0.97]
McGavin 1985	72	0.96 (1.36)	76	1.02 (1.92)		-0.06 [-0.59, 0.47]
Meister 1986	90	1.4 (0)	91	2.95 (0)		0.0 [0.0, 0.0]
Nowak 1999	147	0.35 (0)	148	0.76 (0)		0.0 [0.0, 0.0]
Olivieri 1987	110	0.68 (1.16)	104	1.33 (1.68)		-0.65 [-1.04, -0.26]
Pela 1999	85	0.98 (0.75)	84	1.28 (1.9)		-0.30 [-0.74, 0.14]
Petty 1990	180	6.3 (0)	181	10.2 (0)		0.0 [0.0, 0.0]
Rasmussen 1988	44	1.43 (2.87)	47	1.98 (3.78)		-0.55 [-1.92, 0.82]
Worth 2009	110	0.67 (1.82)	110	0.95 (1.48)		-0.28 [-0.72, 0.16]
Total (95% CI)	**1145**		**1160**			**-0.48 [-0.65, -0.30]**

Heterogeneity: Chi^2 = 19.70, df = 7 (P = 0.01); I^2 =64%

Test for overall effect: Z = 5.41 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 1.13. Comparison 1 Mucolytic versus placebo, Outcome 13 Days on antibiotics per patient per month.

Review: Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease

Comparison: 1 Mucolytic versus placebo

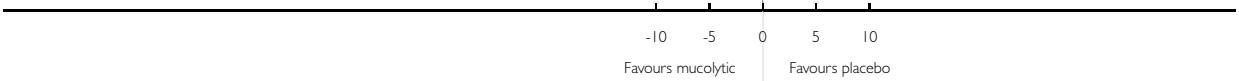
Outcome: 13 Days on antibiotics per patient per month

Study or subgroup	Mucolytic N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Allegra 1996	171	0.63 (1.23)	181	1.05 (1.53)		58.5 %	-0.42 [-0.71, -0.13]
McGavin 1985	72	2.7 (2.88)	76	3.6 (4.88)		3.0 %	-0.90 [-2.18, 0.38]
Olivieri 1987	110	0.57 (1)	104	1.25 (1.58)		38.5 %	-0.68 [-1.04, -0.32]
Total (95% CI)	**353**		**361**			**100.0 %**	**-0.53 [-0.76, -0.31]**

Heterogeneity: Chi^2 = 1.55, df = 2 (P = 0.46); I^2 =0.0%

Test for overall effect: Z = 4.73 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 1.14. Comparison 1 Mucolytic versus placebo, Outcome 14 Health-related quality of life (St George's Respiratory Questionnaire.

Review: Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease

Comparison: 1 Mucolytic versus placebo

Outcome: 14 Health-related quality of life (St George's Respiratory Questionnaire

Study or subgroup	Mucolytic N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Decramer 2005	165	36.7 (16)	146	36.3 (15)		36.5 %	0.40 [-3.05, 3.85]
Worth 2009	110	34.5 (18.9)	110	41.3 (22.5)		27.2 %	-6.80 [-12.29, -1.31]
Zheng 2008	305	37.51 (21.39)	311	42.78 (22.91)		36.3 %	-5.27 [-8.77, -1.77]
Total (95% CI)	**580**		**567**			**100.0 %**	**-3.62 [-8.04, 0.81]**

Heterogeneity: $Tau^2 = 10.85$; $Chi^2 = 7.18$, df = 2 (P = 0.03); $I^2 = 72\%$

Test for overall effect: Z = 1.60 (P = 0.11)

Test for subgroup differences: Not applicable

Analysis 1.15. Comparison 1 Mucolytic versus placebo, Outcome 15 Hospitalisation in the study period.

Review: Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease

Comparison: 1 Mucolytic versus placebo

Outcome: 15 Hospitalisation in the study period

Study or subgroup	mucolytic n/N	placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Decramer 2005	55/256	69/267		80.0 %	0.79 [0.53, 1.18]
Moretti 2004	10/79	19/76		20.0 %	0.45 [0.20, 1.00]
Total (95% CI)	**335**	**343**		**100.0 %**	**0.70 [0.49, 1.01]**

Total events: 65 (mucolytic), 88 (placebo)

Heterogeneity: $Chi^2 = 1.52$, df = 1 (P = 0.22); $I^2 = 34\%$

Test for overall effect: Z = 1.93 (P = 0.054)

Test for subgroup differences: Not applicable

Analysis 1.16. Comparison 1 Mucolytic versus placebo, Outcome 16 FEV1 or % predicted FEV1 or PEFR at end of study.

Review: Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease

Comparison: 1 Mucolytic versus placebo

Outcome: 16 FEV1 or % predicted FEV1 or PEFR at end of study

Study or subgroup	Mucolytic N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Std. Mean Difference IV,Fixed,95% CI
1 Double-blind						
Babolini 1980	234	2.25 (0)	224	2.23 (0)		0.0 [0.0, 0.0]
Boman 1983	92	77.6 (0)	96	77.8 (0)		0.0 [0.0, 0.0]
Bontognali 1991	30	2.49 (0.79)	30	2.14 (0.84)		0.42 [-0.09, 0.94]
Borgia 1981	10	3.54 (0.6)	9	3.05 (1.14)		0.52 [-0.40, 1.44]
Cegla 1988	86	2.45 (0.76)	87	2.45 (0.82)		0.0 [-0.30, 0.30]
Decramer 2005	256	1.6 (0.38)	267	1.6 (0.39)		0.0 [-0.17, 0.17]
Grillage 1985	54	271 (127)	55	252 (92)		0.17 [-0.21, 0.55]
McGavin 1985	85	0.79 (0.35)	96	0.85 (0.37)		-0.17 [-0.46, 0.13]
Moretti 2004	63	1.84 (0.32)	61	1.51 (0.28)		1.09 [0.71, 1.47]
Nowak 1999	33	225.2 (0)	47	61.8 (0)		0.0 [0.0, 0.0]
Olivieri 1987	104	1.94 (0.71)	94	1.88 (0.57)		0.09 [-0.19, 0.37]
Schermer 2009	96	2.07 (0.65)	96	2.12 (0.72)		-0.07 [-0.36, 0.21]
Worth 2009	110	1.7 (0.6)	110	1.61 (0.5)		0.16 [-0.10, 0.43]
Subtotal (95% CI)	**1253**		**1272**			**0.10 [0.01, 0.19]**
Heterogeneity: Chi^2 = 35.35, df = 9 (P = 0.00005); I^2 =75%						
Test for overall effect: Z = 2.14 (P = 0.033)						
2 Single-blind						
Bachh 2007	50	4.6 (1.8)	50	3.9 (1.6)		0.41 [0.01, 0.80]
Pela 1999	83	1.58 (0.63)	80	1.5 (0.56)		0.13 [-0.17, 0.44]
Subtotal (95% CI)	**133**		**130**			**0.24 [-0.01, 0.48]**
Heterogeneity: Chi^2 = 1.15, df = 1 (P = 0.28); I^2 =13%						

(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Mucolytic N	Mucolytic Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Std. Mean Difference IV,Fixed,95% CI
Test for overall effect: Z = 1.91 (P = 0.056)						
Total (95% CI)	**1386**		**1402**		◆	**0.12 [0.03, 0.21]**
Heterogeneity: Chi² = 37.54, df = 11 (P = 0.00009); I² =71%						
Test for overall effect: Z = 2.68 (P = 0.0074)						
Test for subgroup differences: Chi² = 1.04, df = 1 (P = 0.31), I² =4%						

-2 -1 0 1 2

Favours placebo Favours mucolytic

Analysis 1.17. Comparison 1 Mucolytic versus placebo, Outcome 17 FVC at end of study.

Review: Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease

Comparison: 1 Mucolytic versus placebo

Outcome: 17 FVC at end of study

Study or subgroup	Mucolytic N	Mucolytic Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Babolini 1980	234	3.31 (0)	224	3.37 (0)	■	0.0 [0.0, 0.0]
Bontognali 1991	30	3.5 (1)	30	3.07 (1.02)	■	0.43 [-0.08, 0.94]
Borgia 1981	10	4.58 (0.63)	9	4.58 (1.29)	■	0.0 [-0.93, 0.93]
Cegla 1988	86	3.48 (0.79)	87	3.48 (0.88)	■	0.0 [-0.25, 0.25]
McGavin 1985	85	1.89 (0.67)	96	1.89 (0.71)	■	0.0 [-0.20, 0.20]
Olivieri 1987	98	2.99 (0.77)	89	2.95 (0.74)	■	0.04 [-0.18, 0.26]
Schermer 2009	96	3.39 (1)	96	3.36 (1)	■	0.03 [-0.25, 0.31]
Worth 2009	110	2.36 (0.9)	110	2.22 (0.7)	■	0.14 [-0.07, 0.35]
Total (95% CI)	**749**		**741**		◆	**0.06 [-0.04, 0.16]**
Heterogeneity: Chi² = 3.21, df = 6 (P = 0.78); I² =0.0%						
Test for overall effect: Z = 1.16 (P = 0.25)						
Test for subgroup differences: Not applicable						

-2 -1 0 1 2

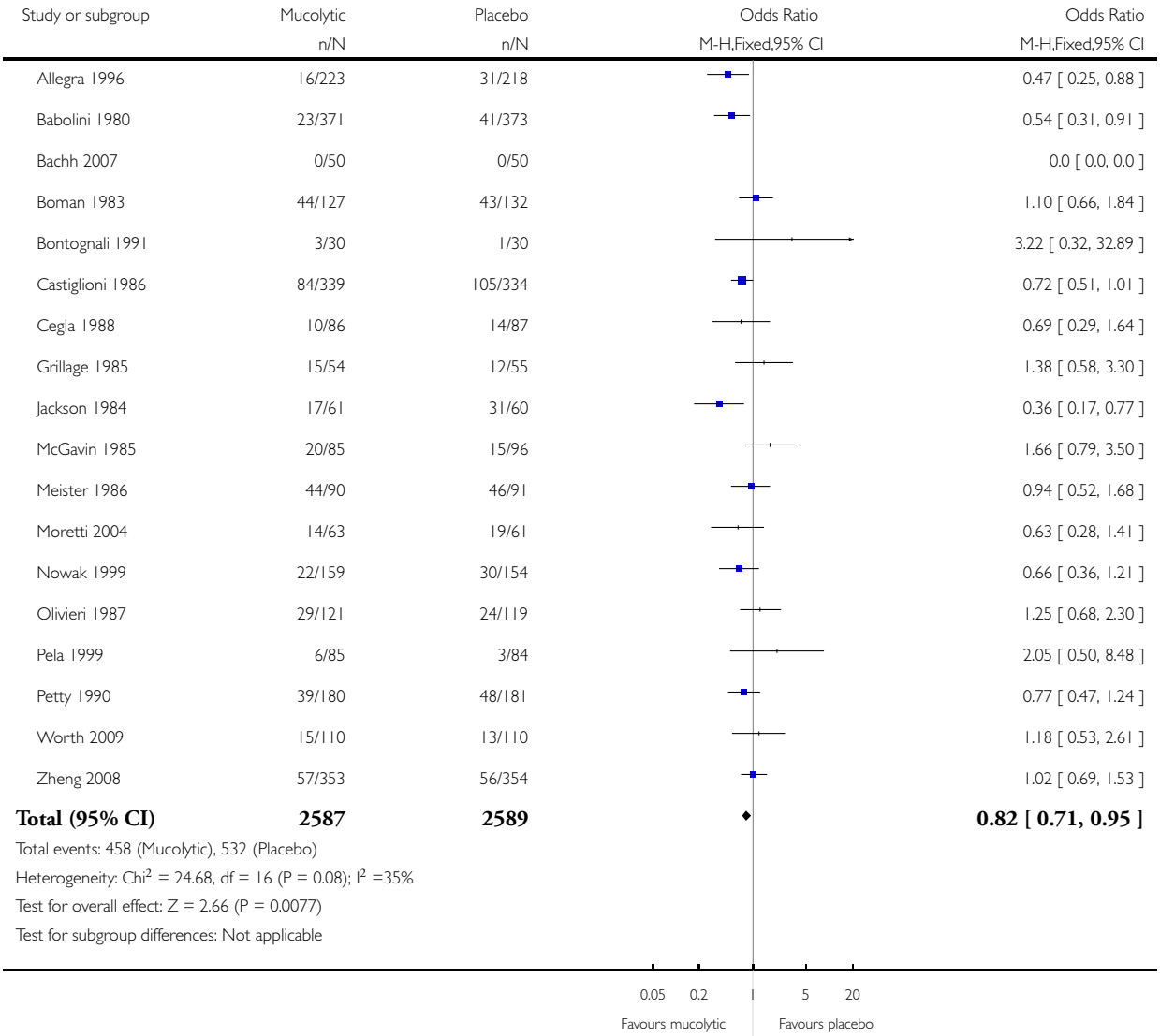
Favours placebo Favours mucolytic

Analysis 1.18. Comparison 1 Mucolytic versus placebo, Outcome 18 Adverse effects.

Review: Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease

Comparison: 1 Mucolytic versus placebo

Outcome: 18 Adverse effects



Analysis 1.19. Comparison 1 Mucolytic versus placebo, Outcome 19 Death during study period.

Review: Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease

Comparison: 1 Mucolytic versus placebo

Outcome: 19 Death during study period

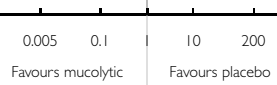
Study or subgroup	mucolytic n/N	placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Jackson 1984	0/61	1/60		0.13 [0.00, 6.71]
Grillage 1985	1/54	1/55		1.02 [0.06, 16.50]
Pela 1999	0/84	1/85		0.14 [0.00, 6.90]
Decramer 2005	9/256	9/267		1.04 [0.41, 2.67]
Zheng 2008	0/353	0/354		0.0 [0.0, 0.0]
Schermer 2009	1/96	3/96		0.36 [0.05, 2.61]
Total (95% CI)	**904**	**917**		**0.75 [0.35, 1.64]**

Total events: 11 (mucolytic), 15 (placebo)

Heterogeneity: Chi^2 = 2.52, df = 4 (P = 0.64); I^2 =0.0%

Test for overall effect: Z = 0.72 (P = 0.47)

Test for subgroup differences: Not applicable



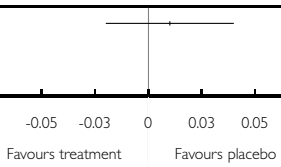
Analysis 2.1. Comparison 2 Systemic thiol donor versus placebo, Outcome 1 Number of exacerbations per patient per month.

Review: Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease

Comparison: 2 Systemic thiol donor versus placebo

Outcome: 1 Number of exacerbations per patient per month

Study or subgroup	Treatment N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Ekberg-Jansson 1999	313	0.18 (0.22)	315	0.17 (0.21)		0.01 [-0.02, 0.04]



Analysis 2.2. Comparison 2 Systemic thiol donor versus placebo, Outcome 2 Patients with no exacerbations in the study period.

Review: Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease

Comparison: 2 Systemic thiol donor versus placebo

Outcome: 2 Patients with no exacerbations in the study period

Study or subgroup	Treatment n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Ekberg-Jansson 1999	174/313	174/315		1.01 [0.74, 1.39]

Analysis 2.3. Comparison 2 Systemic thiol donor versus placebo, Outcome 3 Days of disability per patient per month.

Review: Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease

Comparison: 2 Systemic thiol donor versus placebo

Outcome: 3 Days of disability per patient per month

Study or subgroup	Treatment N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Ekberg-Jansson 1999	313	2.6 (4.03)	315	2.78 (4.15)		-0.18 [-0.82, 0.46]

Analysis 2.4. Comparison 2 Systemic thiol donor versus placebo, Outcome 4 Adverse effects.

Review: Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease

Comparison: 2 Systemic thiol donor versus placebo

Outcome: 4 Adverse effects

Study or subgroup	Treatment n/N	Placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
Ekberg-Jansson 1999	231/313	211/315		1.39 [0.98, 1.95]

ADDITIONAL TABLES

Table 1. Search history

Years	Search result detail
All years to January 1998	We screened approximately 400 abstracts of papers identified from the computer searches. After excluding studies that were clearly ineligible from the abstract, we obtained the full text for 72 papers. There were 21 studies that involved double-blind, placebo-controlled treatment with an oral mucolytic for at least 8 weeks. Three were excluded because they did not provide any information on the primary outcome (Edwards 1976; Maesen 1980; Rubin 1996). Three studies were excluded (Christensen 1971; Grillage 1985; Jackson 1984) because they did not report the standard deviation for the outcome measures of interest and we could not obtain this information despite writing to the authors. Fifteen studies were included in the review
January 1998 to 1999	For the 1999 update there was one further study identified that had been detected on the original search (Cegla 1988) but for which the full text had not been obtained in 1997. Grillage 1985 and Jackson 1984 were not included in the original review but were included in the update as they had data on patients with no exacerbations, an outcome measure that was added for the update. For this update, and until further clarification is obtained from the authors, we have assumed that the error measurement reported in the paper of Olivieri 1987 is an SE rather than SD (see Lung Function).
January 1999 to 2002	In 2002, the search was widened to (chronic bronchitis or emphysema or chronic obstructive pulmonary disease or COPD) AND (mucolytics or mucoactive or N-acetylcysteine or bromhexine or S-carboxymethylcysteine or ambroxol or sobrerol or iodinated glycerol or N isobutyrylcysteine or myrtol or NAC or methylcysteine or carbocysteine or erdosteine or strepronin or gelsolin or MESNA). No further eligible studies were identified by this search
January 2002 to January 2003	In 2003 a repeat search with the same terms yielded 44 titles of which 18 abstracts were screened for eligibility, and five full texts retrieved, none eligible
January 2003-Sept 2005	An update search conducted in 2005 yielded another 264 titles of which nine full texts were retrieved, yielding a further 3 studies for inclusion (Decramer 2005; Malerba 2004; Moretti 2004).
2005-2007	A search in 2005 yielded another 16 titles, none were eligible; in 2006 there were a further 2 titles found with the COOPT study being eligible
2008	Searches in 2008 yielded 20 titles, with 2 more original studies for inclusion (Zheng 2008; Bachh 2007)
May 2011	In 2011, there were 64 abstracts and papers identified from the searches. Several were reports related to the PEACE study (Zheng 2008) and to the EQUALIFE study (Moretti 2004) already included in this review. Of the 7 full texts reviewed, 4 proved eligible: 2 relating to the same study of cineole in COPD (Worth and Worth); another to a further study of cineole (Wilhelmi); one was a further post hoc analysis of EQUALIFE (Ballabio 2008a), One study (Lukas) of NAC in CB was excluded as there were no data on the outcomes in this review Furthermore, we were informed about studies of neltenexine, which is a mucolytic, and considered the full texts of these which were ineligible. Thus there were data from 2 new studies added for the 2012 update (mucolytic* or "mucociliary clearance" or mucoactive or N-acetylcysteine or bromhexine or S-carboxymethylcysteine or ambroxol or sobrerol or "iodinated glycerol" or N isobutyrylcysteine

Table 1. Search history (*Continued*)

	or myrtol or NAC or methylcysteine or carbocysteine or erdosteine or strepronin* or gelsolin or MESNA) In 2011 the above search was run from 2008 to the present date, but with the addition of the term "cineole". We were notified about eligible studies of "neltenexine." This term should be included in the next search
July 2012	In 2012 there were 8 abstracts and papers identified. An abstract (Moretti 2011) was added to studies awaiting classification.

CB: chronic bronchitis
COPD: chronic obstructive pulmonary disease
NAC: N-acetylcysteine

APPENDICES

Appendix 1. Sources and search methods for the Cochrane Airways Group Specialised Register (CAGR)

Electronic searches: core databases

Database	Frequency of search
MEDLINE (Ovid)	Weekly
EMBASE (Ovid)	Weekly
CENTRAL (*The Cochrane Library*)	Quarterly
PsycINFO (Ovid)	Monthly
CINAHL (EBSCO)	Monthly
AMED (EBSCO)	Monthly

Handsearches: core respiratory conference abstracts

Conference	Years searched
American Academy of Allergy, Asthma and Immunology (AAAAI)	2001 onwards
American Thoracic Society (ATS)	2001 onwards
Asia Pacific Society of Respirology (APSR)	2004 onwards
British Thoracic Society Winter Meeting (BTS)	2000 onwards
Chest Meeting	2003 onwards
European Respiratory Society (ERS)	1992, 1994, 2000 onwards
International Primary Care Respiratory Group Congress (IPCRG)	2002 onwards
Thoracic Society of Australia and New Zealand (TSANZ)	1999 onwards

MEDLINE search strategy used to identify trials for the CAGR

COPD search

1. Lung Diseases, Obstructive/
2. exp Pulmonary Disease, Chronic Obstructive/
3. emphysema$.mp.
4. (chronic$ adj3 bronchiti$).mp.
5. (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).mp.
6. COPD.mp.
7. COAD.mp.
8. COBD.mp.
9. AECB.mp.
10. or/1-9

Filter to identify RCTs

1. exp "clinical trial [publication type]"/
2. (randomised or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. Animals/
10. Humans/
11. 9 not (9 and 10)
12. 8 not 11

The MEDLINE strategy and RCT filter are adapted to identify trials in other electronic databases

WHAT'S NEW

Last assessed as up-to-date: 5 July 2012.

Date	Event	Description
5 July 2012	New citation required and conclusions have changed	Conclusions similar, although the beneficial effect of mucolytics on exacerbations in more recent trials is smaller than in the earlier trials
5 July 2012	New search has been performed	Inclusion of two new studies: Worth 2009 (cineole) and Schermer 2009 (N-acetylcysteine (NAC)). Data included from these studies and Decramer 2005 into a new analysis for SGRQ (St George's Respiratory Questionnaire). 'Summary of findings' table added. A third author (CC) was added to the review. A potentially eligible abstract has been added to Studies awaiting classification

HISTORY

Protocol first published: Issue 2, 1996

Review first published: Issue 4, 1998

Date	Event	Description
1 November 2008	New citation required but conclusions have not changed	Review updated to take account of two new studies.
15 September 2008	New search has been performed	Search re-run.
8 August 2008	Amended	Converted to new review format.
10 March 2006	New citation required and conclusions have changed	2005: Repeated search, full update. Inclusion of three new studies, including three-year BRONCHUS study of 600 mg NAC. The effect size of all mucolytics combined is now much smaller than it was, and reasons for this are discussed. In the BRONCHUS study there was a significant effect of NAC on exacerbations seen in those participants not on inhaled corticosteroids. A new comparison has been added to address this.

(*Continued*)

		Other new comparisons added: hospitalisations, deaths. Otherwise findings remain much the same as previously.
1 August 2002	New search has been performed	2002: No new studies were found despite a wider search strategy. The discussion has been expanded to include information on other recent meta-analyses of NAC and a comparison of the effects of mucolytics and fluticasone on exacerbations. Jadad scores for studies are now included. The data and conclusions remain the same as in 1999.
31 August 1999	New search has been performed	1999: The review now includes two studies in COPD patients, hence the title change. It also includes data on two other agents, myrtol and the thiol donor N-isobutyrylcysteine. Eight more studies are included and several more analyses. There is a correction to the reviewers' conclusions about the effect of mucolytics on the secondary endpoint of lung function. We have checked our extraction of the data as presented in the original data and these are correct. However, we have concerns about the small standard deviations in the Olivieri study and suspect that the authors reported standard errors. Indeed, the P values that they quote in their analysis would be compatible with this conclusion. Until this is clarified we have removed this trial from the analysis. The analysis of the lung function data now shows no significant change in lung function (this had previously been interpreted as favouring placebo). Changes have been made in the relevant parts of the Abstract, Results (Lung Function) and Discussion sections. The overall conclusions of this review with respect to the primary endpoint of exacerbation frequency and days of disability ('sick days') do not change. We cannot explain the high level of heterogeneity in the size of this effect between trials and in a future version of this review will examine the possibility that it is due to the length of the study. In the adverse effects analysis the Parr and Rasmussen data have been taken out of the meta-analysis and reported instead in the text. This is because the event

(*Continued*)

		rates in these studies exceeded the numbers in the treatment groups. RevMan is unable to manage dichotomous data where the event rate exceeds one. The meta-analysis suggests that adverse effects may be less frequent in the mucolytic-treated group. However, in the large study by Parr (n = 526), there was a mean of 4.9 adverse effects per participant in the mucolytic group, versus 4.5 adverse effects per participant in the placebo group. We have, therefore, not changed our original conclusion that there is no difference between treatments in terms of adverse effects

CONTRIBUTIONS OF AUTHORS

Dr Phillippa Poole has had the primary overall responsibility for this review throughout its iterations. Until his death in 2010, Dr Black contributed to all aspects of the review, including approval of the final version of the substantive updates in 1999, 2002, 2005, 2006 and 2008. Dr Chris Cates has provided support for the review from inception and has assisted with the analysis, interpretation, data-checking and write-up of the 2012 update.

DECLARATIONS OF INTEREST

No financial support was received for this review and there is no conflict of interest.

SOURCES OF SUPPORT

Internal sources

- No support received, Not specified.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This review has used a modified version of the full 'Risk of bias' tool described in chapter 8 of the Cochrane Handbook. The protocol and initial review versions used Jadad scores to assess trial quality. We have retained the original scores from the Jadad scoring system, but report our judgements of the risk of bias for procedures relating to allocation concealment.

Additional outcomes added for updates from 2006 to 2012:

1. Hospitalisation and mortality (added as outcomes for the 2006 and 2008 updates)
2. Quality of life (added for the 2008 update, with a meta-analysis of SGRQ scores included in the 2012 update)

The Jadad scores for individual studies are reported in Characteristics of included studies. Each study was assessed using the 0 to 5 scale described by Jadad 1996, as summarised below:

1. Was the study described as randomised? (1 = yes; 0 = no)
2. Was the study described as double-blind? (1 = yes; 0 = no)
3. Were withdrawals and dropouts described? (1 = yes; 0 = no)
4. Was the method of randomisation well-described and appropriate? (1 yes; 0 = no)
5. Was the double-blinding well-described and appropriate? (1 = yes; 0 = no)
6. Deduct 1 point if methods for randomisation or blinding were inappropriate.

Double-blinding was not an inclusion criteria.

INDEX TERMS

Medical Subject Headings (MeSH)

Bronchitis [*drug therapy; prevention & control]; Chronic Disease; Disease Progression; Expectorants [* therapeutic use]; Lung Diseases, Obstructive [*drug therapy; prevention & control]; Numbers Needed To Treat; Quality of Life; Randomized Controlled Trials as Topic

MeSH check words

Adult; Humans