Cochrane Library

Cochrane Database of Systematic Reviews

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

Poole P, Chong J, Cates CJ

Poole P, Chong J, Cates CJ.
Mucolytic agents versus placebo for chronic bronchitis or chronic obstructive pulmonary disease.
Cochrane Database of Systematic Reviews 2015, Issue 7. Art. No.: CD001287.
DOI: 10.1002/14651858.CD001287.pub5.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

HEADER . . . 1
ABSTRACT . . . 1
PLAIN LANGUAGE SUMMARY . . . 2
SUMMARY OF FINDINGS FOR THE MAIN COMPARISON . . . 3
BACKGROUND . . . 5
OBJECTIVES . . . 5
METHODS . . . 5
RESULTS . . . 7
Figure 1. . . . 8
Figure 2. . . . 11
Figure 3. . . . 12
Figure 4. . . . 13
Figure 5. . . . 14
DISCUSSION . . . 17
Figure 6. . . . 19
AUTHORS' CONCLUSIONS . . . 22
ACKNOWLEDGEMENTS . . . 22
REFERENCES . . . 23
CHARACTERISTICS OF STUDIES . . . 27
DATA AND ANALYSES . . . 61
Analysis 1.1. Comparison 1 Mucolytic versus placebo, Outcome 1 Participants with no exacerbations in study period. 63
Analysis 1.2. Comparison 1 Mucolytic versus placebo, Outcome 2 Participants with no exacerbation by decade, db trials only. . . . 65
Analysis 1.3. Comparison 1 Mucolytic versus placebo, Outcome 3 Participants with no exacerbations in the study period - winter treatment only. . . . 67
Analysis 1.4. Comparison 1 Mucolytic versus placebo, Outcome 4 Number of exacerbations per participant per month. 69
Analysis 1.5. Comparison 1 Mucolytic versus placebo, Outcome 5 Number of exacerbations per participant per month, by type or dose of mucolytic. . . . 71
Analysis 1.6. Comparison 1 Mucolytic versus placebo, Outcome 6 Number of exacerbations per participant per month, by FEV1. . . . 74
Analysis 1.7. Comparison 1 Mucolytic versus placebo, Outcome 7 Number of exacerbations per participant per month, no ICS. . . . 75
Analysis 1.8. Comparison 1 Mucolytic versus placebo, Outcome 8 Number of exacerbations per participant per month, by study duration. . . . 76
Analysis 1.9. Comparison 1 Mucolytic versus placebo, Outcome 9 Number of exacerbations per participant per month, by country. . . . 78
Analysis 1.10. Comparison 1 Mucolytic versus placebo, Outcome 10 Number of exacerbations per participant per month, in participants included for history of exacerbation. . . . 80
Analysis 1.11. Comparison 1 Mucolytic versus placebo, Outcome 11 Days of disability per participant per month. . 81
Analysis 1.12. Comparison 1 Mucolytic versus placebo, Outcome 12 Days on antibiotics per participant per month. 82
Analysis 1.13. Comparison 1 Mucolytic versus placebo, Outcome 13 Health-related quality of life (total score St George Respiratory Questionnaire). . . . 83
Analysis 1.14. Comparison 1 Mucolytic versus placebo, Outcome 14 Hospitalisation during study period. . . . 84
Analysis 1.15. Comparison 1 Mucolytic versus placebo, Outcome 15 FEV1 or % predicted FEV1 or PEFR at end of study. . . . 85
Analysis 1.16. Comparison 1 Mucolytic versus placebo, Outcome 16 FVC at end of study. . . . 86
Analysis 1.17. Comparison 1 Mucolytic versus placebo, Outcome 17 Adverse effects. . . . 87
Analysis 1.18. Comparison 1 Mucolytic versus placebo, Outcome 18 Death during study period. . . . 88
Analysis 2.1. Comparison 2 Systemic thiol donor versus placebo, Outcome 1 Number of exacerbations per participant per month. . . . 89

Analysis 2.2. Comparison 2 Systemic thiol donor versus placebo, Outcome 2 Participants with no exacerbations in the study period. 89
Analysis 2.3. Comparison 2 Systemic thiol donor versus placebo, Outcome 3 Days of disability per participant per month. 90
Analysis 2.4. Comparison 2 Systemic thiol donor versus placebo, Outcome 4 Adverse effects. 90
APPENDICES 90
WHAT'S NEW 94
HISTORY 95
CONTRIBUTIONS OF AUTHORS 97
DECLARATIONS OF INTEREST 97
SOURCES OF SUPPORT 97
DIFFERENCES BETWEEN PROTOCOL AND REVIEW 98
INDEX TERMS 98

[Intervention Review]

Mucolytic agents versus placebo for chronic bronchitis or chronic obstructive pulmonary disease

Phillippa Poole[1], Jimmy Chong[2], Christopher J Cates[3]

[1]Department of Medicine, University of Auckland, Auckland, New Zealand. [2]University of Auckland, Auckland, New Zealand. [3]Population Health Research Institute, St George's, University of London, London, UK

Contact address: Phillippa Poole, Department of Medicine, University of Auckland, Private Bag 92019, Auckland, New Zealand. p.poole@auckland.ac.nz.

Editorial group: Cochrane Airways Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 7, 2015.
Review content assessed as up-to-date: 3 July 2014.

Citation: Poole P, Chong J, Cates CJ. Mucolytic agents versus placebo for chronic bronchitis or chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews* 2015, Issue 7. Art. No.: CD001287. DOI: 10.1002/14651858.CD001287.pub5.

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. Personal and healthcare costs associated with exacerbations indicate that any therapy that reduces the occurrence of exacerbations is useful. A marked difference among countries in terms of prescribing of mucolytics reflects variation in perceptions of their effectiveness.

Objectives

Primary objective

• To determine whether treatment with mucolytics reduces frequency of exacerbations and/or days of disability in patients with chronic bronchitis or chronic obstructive pulmonary disease.

Secondary objectives

• To assess whether mucolytics lead to improvement in lung function or quality of life.

• To determine frequency of adverse effects associated with use of mucolytics.

Search methods

We searched the Cochrane Airways Group Specialised Register and reference lists of articles on 10 separate occasions, most recently in July 2014.

Selection criteria

We included randomised studies that compared oral mucolytic therapy versus 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

This review analysed summary data only, most derived from published studies. For earlier versions, one review author extracted data, which were rechecked in subsequent updates. In later versions, review authors double-checked extracted data and then entered data into RevMan for analysis.

Main results

We added four studies for the 2014 update. The review now includes 34 trials, recruiting a total of 9367 participants. Many studies did not clearly describe allocation concealment; hence selection bias may have inflated the results, which reduces our confidence in the findings.

Results of 26 studies with 6233 participants show that the likelihood that a patient could be exacerbation-free during the study period was greater among mucolytic groups (Peto odds ratio (OR) 1.75, 95% confidence interval (CI) 1.57 to 1.94). However, more recent studies show less benefit of treatment than was reported in earlier studies in this review. The overall number needed to treat with mucolytics for an additional beneficial outcome for an average of 10 months - to keep an additional participant free from exacerbations - was eight (NNTB 8, 95% CI 7 to 10). Use of mucolytics was associated with a reduction of 0.03 exacerbations per participant per month (mean difference (MD) -0.03, 95% CI -0.04 to -0.03; participants = 7164; studies = 28; I^2 = 85%) compared with placebo, that is, about 0.36 per year, or one exacerbation every three years. Very high heterogeneity was noted for this outcome, so results need to be interpreted with caution. The type or dose of mucolytic did not seem to alter the effect size, nor did the severity of COPD, including exacerbation history. Longer studies showed smaller effects of mucolytics than were reported in shorter studies.

Mucolytic use was associated with a reduction of 0.43 days of disability per participant per month compared with placebo (95% CI -0.56 to -0.30; studies = 13; I^2 = 61%). With mucolytics, the number of people with one or more hospitalisations was reduced, but study results were not consistent (Peto OR 0.68, 95% CI 0.52 to 0.89; participants = 1788; studies = 4; I^2 = 58%). Investigators reported improved quality of life with mucolytics (MD -2.64, 95% CI -5.21 to -0.08; participants = 2231; studies = 5; I^2 = 51%). Although this mean difference did not reach the minimal clinically important difference of -4 units, we cannot assess the population impact, as we do not have the data needed to carry out a responder analysis. Mucolytic treatment was not associated with any significant increase in the total number of adverse effects, including mortality (Peto OR 1.03, 95% CI 0.52 to 2.03; participants = 2931; studies = 8; I^2 = 0%), but the confidence interval is too wide to confirm that the treatment has no effect on mortality.

Authors' conclusions

In participants with chronic bronchitis or COPD, we are moderately confident that treatment with mucolytics may produce a small reduction in acute exacerbations and a small effect on overall quality of life. Our confidence in the results is reduced by the fact that effects on exacerbations shown in early trials were larger than those reported by more recent studies, possibly because the earlier smaller trials were at greater risk of selection or publication bias, thus benefits of treatment may not be as great as was suggested by previous evidence.

PLAIN LANGUAGE SUMMARY

Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease

Mucolytics are medicines taken orally that may loosen sputum, making it easier to cough it up. Mucolytics may have other beneficial effects on lung infection and inflammation and may be useful in the treatment of people with chronic obstructive pulmonary disease (COPD) or chronic bronchitis. This review assessed how effective they were in these patients. Review authors looked at 34 studies with a total of 9367 patients. Results showed a small reduction in the number of exacerbations (worsening of disease/symptoms) experienced by the patient if the medication was taken on a regular basis - that is, approximately one less patient with an exacerbation for every eight treated with a mucolytic over 10 months. However, this review includes a mix of small older studies and large newer ones, with newer ones showing less benefit. The medicines appear to be safe and well tolerated; however we are unsure about their impact on quality of life and on risk of hospitalisation.

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
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Mucolytic				
Participants with no exacerbations in study period Follow-up: 2 to 36 months	**389 per 1000**	**527 per 1000** (499 to 552)	**OR 1.75** (1.57 to 1.94)	6233 (26 studies)	⊕⊕◯◯ **Low**[a,b]	Mean follow-up 10 months Larger effects in earlier studies of mucolytics in chronic bronchitis. Smaller effects in more recent studies in COPD
Number of exacerbations per participant per month Follow-up: 2 to 36 months	Mean number of exacerbations per participant per month in control group was 0.2	Mean number of exacerbations per participant per month in intervention group was 0.03 lower (0.04 lower to 0.03 lower)	-	7164 (28 studies)	⊕⊕⊕◯ **Moderate**[a,c]	Effect size slowly reducing as more studies are added
Health-related quality of life (total score on SGRQ) Follow-up: 2 to 36 months	Mean health-related quality of life score (total score St George Respiratory Questionnaire) in control group was 40	Mean health-related quality of life score (total score St George Respiratory Questionnaire) in intervention group was 2.64 lower (5.21 lower to 0.08 lower)	-	2231 (5 studies)	⊕⊕⊕◯ **Moderate**[d,e]	Total score is score out of 100 derived from 3 subscales Lower scores are better. A well person with no respiratory disease scores is about 7. Minimum clini-

						cally important difference is 4
Hospitalisations Follow-up: 2 to 36 months	**188 per 1000**	**136 per 1000** (107 to 171)	**OR 0.68** (0.52 to 0.89)	1788 (4 studies)	⊕⊕⊕◯ **Moderate**[d,e]	124 admissions on mucolytics and 169 on placebo
Adverse effects Follow-up: 2 to 36 months	**211 per 1000**	**190 per 1000** (172 to 211)	**OR 0.88** (0.78 to 1.00)	6346 (21 studies)	⊕⊕◯◯ **Low**[a,b]	Total adverse effects reported. All adverse effects mild and self limiting
Death during study period Follow-up: 2 to 36 months	**12 per 1000**	**12 per 1000** (6 to 23)	**OR 1.03** (0.52 to 2.03)	2931 (8 studies)	⊕⊕◯◯ **Low**[d,f]	17 deaths on mucolytics and 17 deaths on placebo

*The basis for the **assumed risk** is the weighted mean control group risk across studies. 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.

[a] (-1 limitations) Most trials at risk of selection bias (see Figure 6).
[b] (-1 limitations) Inconsistent results between trials; more recent trials show smaller treatment effects.
[c] Smaller treatment effects in more recent trials, but clinical significance of the estimate is unlikely to be changed by future research.
[d] Few studies contribute data to this outcome, but they were generally more recent studies at lower risk of bias.
[e] (-1 heterogeneity) Important variability between results of studies.
[f] (-2 imprecision) Results include possibility of a large difference in either direction.

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 for 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 2015), 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 to noxious particles or gases in the airways and the lung. Exacerbations and comorbidities contribute to overall severity in individual patients.

It is estimated that COPD is the fourth or fifth most common single cause of death worldwide. Currently no cure for COPD is known, although it is 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 2015).

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 increased breathlessness or 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 are the largest contributor to healthcare costs in COPD (Criner 2015). Thus, treatments that reduce the frequency and duration of acute exacerbations will provide benefits for both individual patients and healthcare systems.

How the intervention might work

Mucolytics are oral medicines that are believed to increase expectoration of sputum by reducing its viscosity, thus making it easier to cough it up. Given that oxidative stress is thought to be an amplifying mechanism in COPD (Rahman 2005), a property of mucolytics such as N-acetylcysteine that may be useful in chronic airways disease is an 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 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 theoretical reasons have been proposed to explain why mucolytics may work in both chronic bronchitis and COPD, and because treatments that reduce exacerbations are needed to reduce morbidity and costs, this review will seek to determine the true effect of this class of medicines.

OBJECTIVES

Primary objective

- To determine whether treatment with mucolytics reduces frequency of exacerbations and/or days of disability in patients with chronic bronchitis or COPD.

Secondary objectives

- To assess whether mucolytics lead to improvement in lung function or quality of life.
- To determine the frequency of adverse effects associated with use of mucolytics.

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 studies of 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 longer than two successive years) or COPD as defined by the criteria of the American Thoracic Society, the Global Initiative for Chronic Obstructive Lung Disease (GOLD), the European Respiratory Society or the World Health Organization (WHO). We excluded studies on patients with asthma or cystic fibrosis.

Types of interventions

Participants must have received regular treatment with oral mucolytics or 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. The 1999 update of this review included two studies of newer agents: 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

- Exacerbations, as measured by the number of participants with no exacerbations during the study period, as well as the total number of acute exacerbations per participant.

Exacerbation was defined as an increase in cough and by volume and/or purulence of sputum.

- Number of days of disability variously defined as days in bed, days off work or days on which the participant was unable to undertake normal activities. We also assessed days on antibiotics.

Secondary outcomes

- Measures of lung function, including forced expiratory volume in one second (FEV_1), forced vital capacity (FVC) and peak expiratory flow rate (PEFR).
- Adverse effects of treatment.
- Hospitalisation and mortality.
- Quality of life as measured by a tool validated in patients with COPD.

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 symptom scores.

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

Search methods for identification of studies

Electronic searches

Search methods and search history for previous versions of this review are detailed in Appendix 1. The previous published version included searches up to July 2012. The search period for this update is July 2012 through July 2014.

We identified studies using the Cochrane Airways Group Specialised Register of trials (CAGR), which is derived through systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and the Cumulative Index to Nursing and Allied Health Literature (CINAHL), and by handsearching of respiratory journals and meeting abstracts (see Appendix 2 for details). We searched for relevant trials in the CAGR using the search strategy presented in Appendix 3. We did not apply restrictions on language or type of publication.

Searching other resources

We checked the references of all papers and reviews for which we obtained the full text to identify other relevant articles. We asked other researchers in the field to provide additional references, and we remained open to unsolicited suggestions regarding potentially eligible studies. For the 2014 update, we searched these online clinical trials registers: ClinicalTrials.gov (www.ClinicalTrials.gov) and the WHO trials portal (www.who.int/ictrp/en/).

Data collection and analysis

Selection of studies

At least one review author (Peter Black and PP for original review, PP and JC for updates) assessed all abstracts obtained from the search of the CAGR. We obtained the full text for those that appeared to fit the criteria for inclusion (or if this was not clear from the abstract). Two review authors independently selected trials for inclusion in the original review and updates and resolved disagreements over inclusion by discussion. Six translators (two of whom were medically trained) assessed papers published in languages other than English. For the last two updates, the review lead author (PP) was assisted by another Cochrane review author (JC) in extracting data.

Data extraction and management

We abstracted data onto worksheets before entering them into the Review Manager software (RevMan 5.3). We double-checked all entries against the original paper. In the 1999 update, we rechecked all data from earlier studies.

Assessment of risk of bias in included studies

We used the following to assess sources of bias in selection, allocation, performance, detection, attrition or reporting.

- Low risk of bias.

- Unclear risk of bias: if insufficient information was available.
- High risk of bias.

Measures of treatment effect

We analysed continuous data using mean differences (MDs) (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 (SMDs). We used Peto odds ratios (ORs) for dichotomous data and reported results with 95% confidence intervals (CIs).

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 participant per month). We scaled standard deviations for monthly rates in the same way.

Dealing with missing data

If data were insufficient, we requested further information by writing to the study author or to the pharmaceutical company sponsoring the study.

Assessment of heterogeneity

We used the I^2 statistic to measure heterogeneity among the trials in each analysis. We reported cases of substantial heterogeneity and explored possible causes by performing prespecified subgroup analysis.

Assessment of reporting biases

When we were able to pool more than 10 trials, we created and examined a funnel plot to explore possible small study and publication biases.

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 for an additional beneficial outcome (NNTB) based on the pooled Peto odds ratio (Cates 2002), with baseline risk taken from the pooled control group event rate (total number of events divided by overall number of participants in the placebo group multiplied by 100).

Subgroup analysis and investigation of heterogeneity

From the outset, we planned a priori subgroup analyses based on type of mucolytic, dose, duration, country of study, disease severity and whether or not participants were included, as they had a history of exacerbation.

Following publication of the BRONCUS study (Decramer 2005), which suggested a differential effect of mucolytics depending on concomitant treatment, we included an analysis on whether concomitant inhaled corticosteroids were permitted.

From 2012 onwards, we carried out a post hoc investigation of time trends in data on participants with one or more exacerbations by comparing results of trials published since 2000 versus those published earlier.

Sensitivity analysis

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

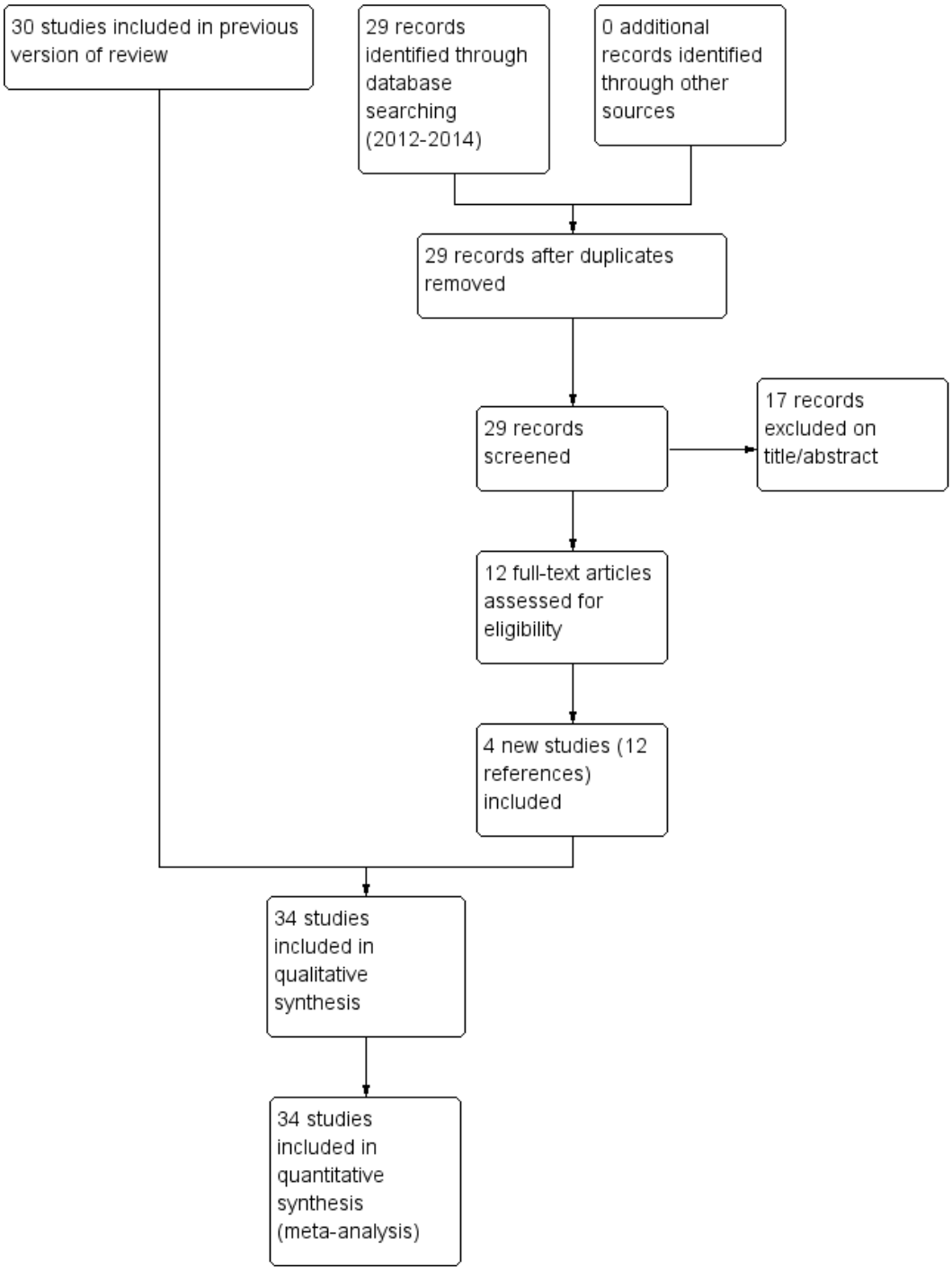
RESULTS

Description of studies

Results of the search

For details of the search history, see Appendix 1, and for the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) study flow diagram for this update, see Figure 1. More than 793 abstracts have been identified through iterative computer searches. After excluding studies that were clearly ineligible, we reviewed the full texts of 108 papers.

Figure 1. Study flow diagram: review update.



The 2014 search yielded 29 abstracts, as well as four new eligible studies - all of NAC versus placebo. Four abstracts related to the eligible study of Zheng 2014, four to Tse 2013, three to De Backer 2013 and one to Roy 2014. We found a total of 17 reports of ineligible studies, including Moretti 2011, which in 2012 was awaiting classification. We found a further report of the Roy study while searching for study authors' contact details. Searches of online clinical trials databases yielded no further studies.

In the initial review in 1997, 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) to request more information. We received further data for two studies (Allegra 1996; Nowak 1999). Dr Petty responded to our letter but could not supply data because they were held by a pharmaceutical company (the company has not replied to two letters). Dr Boman wrote to say that he was unable to supply us with additional data. This was also the case for Novartis Pharmaceuticals (UK), which responded on behalf of two study authors (Jackson 1984; Parr 1987), and Parke Davis Research Laboratories (Grillage 1985). We received no reply to our request for additional data related to the remaining three studies (Babolini 1980; Castiglioni 1986; Christensen 1971), although we sent two letters. We also wrote to the authors of Olivieri 1987 to clarify the error measurement used, but we 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), which was 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; the lead author helpfully provided us with information derived from the St George's Respiratory Questionnaire (SGRQ).

in 2014, we wrote to Dr De Backer to request additional details on the secondary outcomes of spirometry and quality of life (De Backer 2013) but received no response. As this was a small cross-over study with few outcomes of relevance to this review, we have not pursued this. Dr Zheng provided the appendix to Zheng 2014, which contained further details on study design and outcomes. In response to another request, Dr Zheng provided standard deviations (SDs) of exacerbation rates and total SGRQ, as well as mean (SD) end of study FEV_1 and FVC values.

Included studies

By 2015, this review included 34 RCTs, which had recruited a total of 9367 participants. We provide full details of each study in Characteristics of included studies.

A total of 12 studies (Bachh 2007; De Backer 2013; Decramer 2005; Malerba 2004; Moretti 2004; Nowak 1999; Pela 1999; Roy 2014; Tse 2013; Worth 2009; Zheng 2008; Zheng 2014) examined use of mucolytics in people with COPD. A study in primary care included participants with chronic bronchitis and/or COPD (Schermer 2009). The other studies involved people with chronic bronchitis.

All but four studies were randomised, double-blind and placebo-controlled and used a parallel-group design. Study duration ranged from 2 to 36 months. Twelve 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; Tse 2013; Zheng 2008; Zheng 2014). Four studies were described as randomised and placebo-controlled but not as double-blind. One of these was labelled as 'open' (Pela 1999), and two (Bachh 2007; Roy 2014) were 'single-blind' trials. The fourth (De Backer 2013) was a randomised cross-over trial. As a result of the potential for bias, these are reported separately in analyses of primary outcomes.

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

Inclusion and exclusion criteria

All studies indicated that 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 whether patients with other respiratory illnesses were excluded.

Lung function

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

Age of participants

The mean age of participants ranged from 40 to 71 years. Most studies had an upper age limit for participants.

Gender of participants

All but three of the studies reported the proportion of males included in the study. This ranged from 44% to 93%. In another study, "almost all" of the participants were reported as male.

Smokers

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

Mucolytics and dose

In 19 studies, the mucolytic used was N-acetylcysteine (NAC). Other treatments studied included carbocysteine (N = 4), ambroxol (N = 3), sobrerol, letosteine, cithiolone, iodinated glycerol, N-isobutyrylcysteine (NIC), myrtol, erdosteine and cineole.
Of the 19 studies of NAC, three used a total dose of 400 mg/d (Babolini 1980; Boman 1983; Borgia 1981); 11 used a total dose of 600 mg/d (Bachh 2007; Decramer 2005; Grassi 1976; Jackson 1984; McGavin 1985; Meister 1986; Nowak 1999; Parr 1987; Pela 1999; Rasmussen 1988; Schermer 2009); three used 1200 mg/d (Hansen 1994; Roy 2014; Tse 2013); and two used 1800 mg/d (De Backer 2013; Zheng 2014).

Size and duration

Study size ranged from 12 (De Backer 2013) to 1004 (Zheng 2014) participants. Duration ranged from 2 months (Petty 1990) to 36 months (Decramer 2005; Schermer 2009). The mean duration of treatment, weighted by study size, was 9.6 months. A third of participants were enrolled in studies lasting 12 months or longer.

Countries

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

Excluded studies

See Characteristics of excluded studies for the reasons for exclusion.

Risk of bias in included studies

Allocation

Potential for bias in most studies was regarded as unclear, in that study authors stated that the study was randomised but did not indicate how this was achieved, where it was done or how it was concealed. The BRONCUS (Decramer 2005), PEACE (Zheng 2008), COOPT (Schermer 2009) and PANTHEON (Zheng 2014) studies were graded as low risk, as the method of concealment of randomisation was carefully outlined and appropriate. In six studies (Bachh 2007; Boman 1983; Castiglioni 1986; De Backer 2013; Pela 1999; Roy 2014), concealment was regarded as high risk. Most studies reported 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. Five studies were regarded as high risk, which related largely to lack of blinding (Bachh 2007; De Backer 2013; Pela 1999; Roy 2014; Worth 2009).

Incomplete outcome data

Reported dropout ranged from 0% (Bachh 2007; Bontognali 1991; Cremonini 1986) to 37% in the three-year BRONCUS study (Decramer 2005), and was given as 43% in another three-year study conducted in a general practice setting (Schermer 2009). When the rate exceeded 20%, we graded this as high risk (15 studies) (Allegra 1996; Bachh 2007; Boman 1983; Decramer 2005; Ekberg-Jansson 1999; Jackson 1984; McGavin 1985; Meister 1986; Moretti 2004; Parr 1987; Petty 1990; Rasmussen 1988; Roy 2014; Schermer 2009; Zheng 2014).
In most of the older studies and in Roy 2014, analyses were performed on participants who completed the study (per protocol), whereas in more recent studies, analyses tended to be performed on an intention-to-treat basis.

Selective reporting

Three studies were graded as high risk: two because they were unpublished (Meister 1986; Nowak 1999) and one because study authors did not report all study outcomes (De Backer 2013).

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 during study period

The odds ratio (OR) for having no exacerbations over the entire study period when treatment with mucolytics was provided in double-blind trials was increased compared with placebo (Peto OR 1.75, 95% confidence interval (CI) 1.57 to 1.94; Figure 2; Analysis 1.1). This yielded a number needed to treat for an additional beneficial outcome (NNTB) of 8 (95% CI 7 to 10; Figure 3). However, as heterogeneity in this result is high (I^2 =

63%), we carried out a post hoc subgroup analysis showing results of double-blind trials by decade of publication (Analysis 1.2; Figure 4). This revealed a tendency for more recent studies to provide more conservative results: 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) have a greater effect size than those published since 2000 (Peto OR 1.21, 95% CI 1.03 to 1.43). It is also notable that the four studies with adequate allocation concealment (Decramer 2005; Schermer 2009; Zheng 2008. Zheng 2014) did not report a major benefit of treatment in preventing exacerbations.

Figure 2. Forest plot of comparison: 1 Mucolytic versus placebo, outcome: 1.1 Participants with no exacerbations in study period.

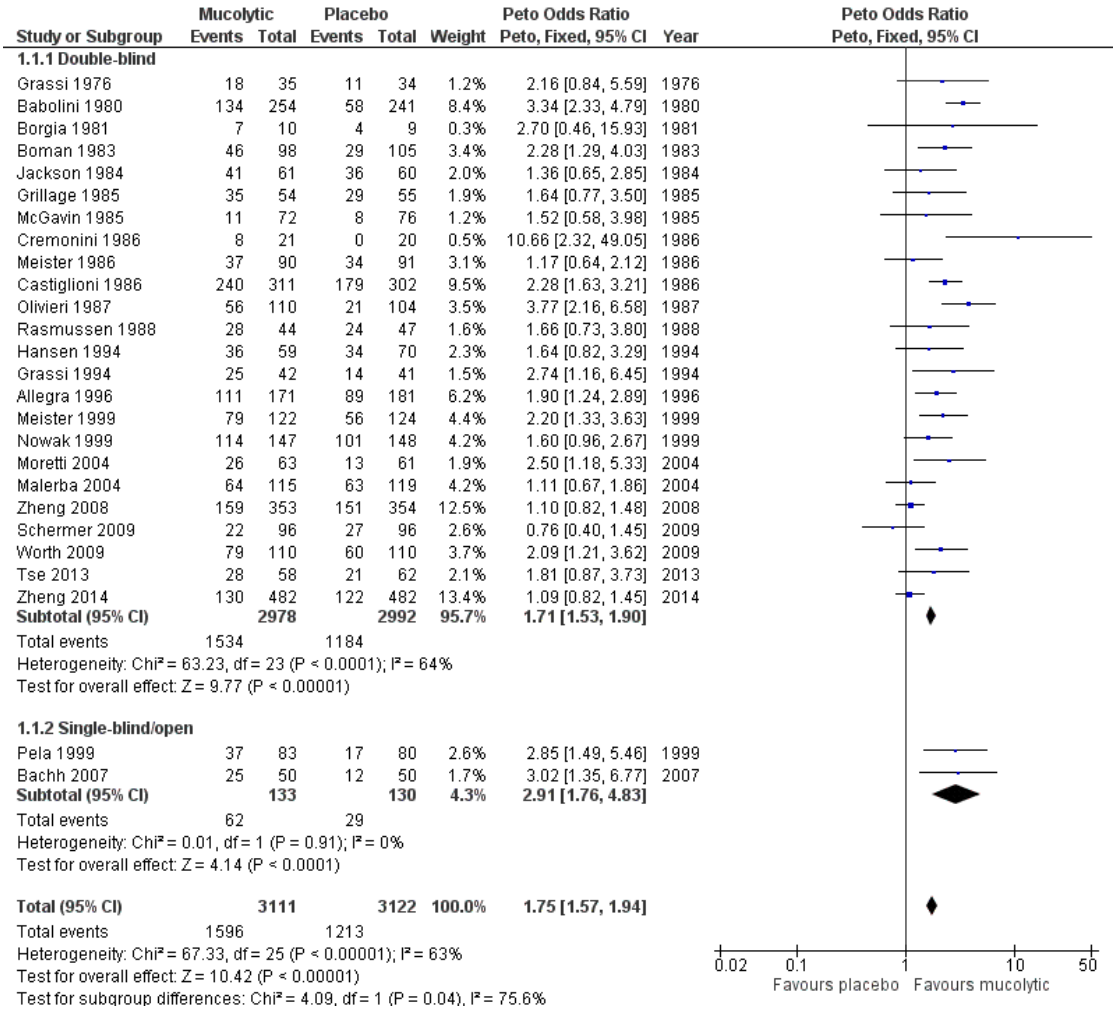


Figure 3. In the control group, 39 of 100 people were free from exacerbations over 10 months (represented by green faces) compared with 53 (95% CI 50 to 55) of 100 for the mucolytic group (represented by green plus yellow faces).

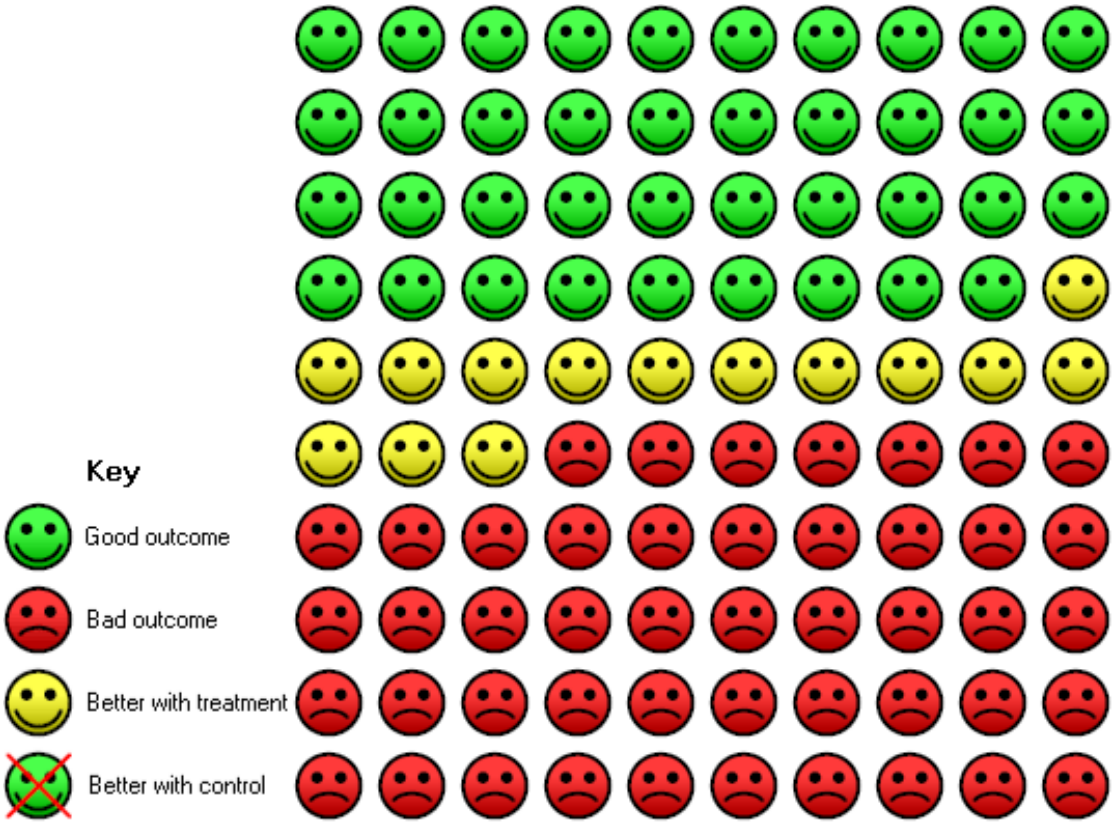
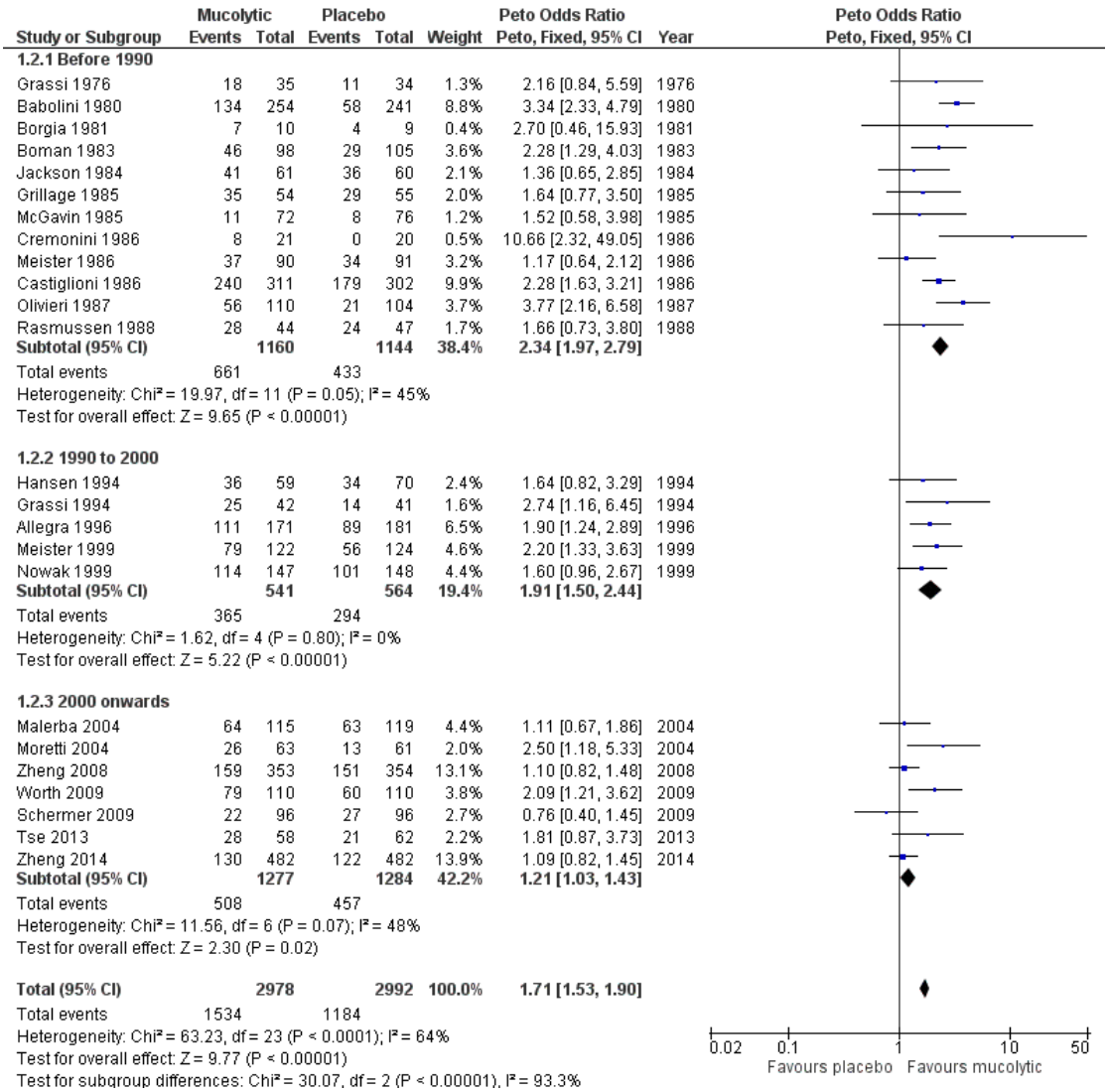
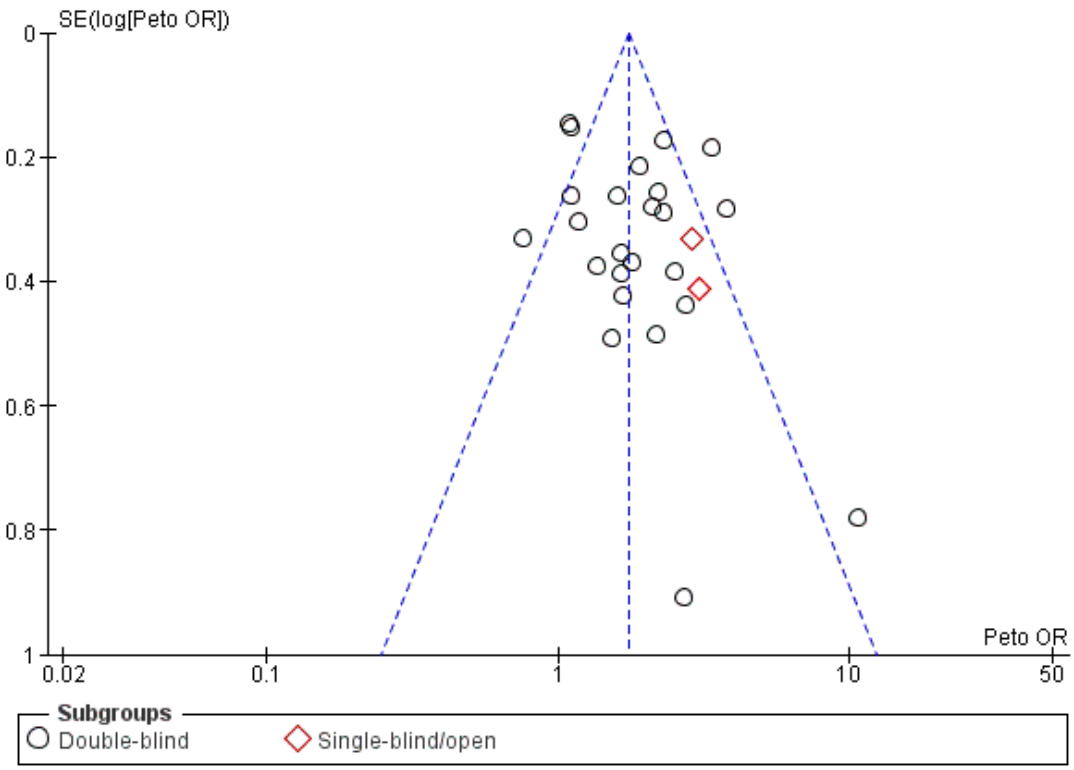


Figure 4. Forest plot of comparison: 1 Mucolytic versus placebo, outcome: 1.2 Participants with no exacerbation by decade, db trials only.



Furthermore, inspection of the funnel plot in Figure 5 suggests the possibility of 'small study' effects, as no small studies show negative outcomes. This raises the possibility that some negative small studies may not have been published, and publication bias could lead to overestimation of the benefits of treatment for exacerbations.

Figure 5. Funnel plot of comparison: 1 Mucolytic versus placebo, outcome: 1.1 Participants with no exacerbations in study period.



If the analysis is conducted only on studies conducted over eight months during winter, the effect is larger, with an odds ratio of 2.20 (95% CI 1.93 to 2.51; P value < 0.00001; Analysis 1.3).

Number of exacerbations per participant per month

Use of mucolytics was associated with a reduction of 0.03 exacerbations per participant per month (95% CI -0.04 to -0.03; Analysis 1.4). These results need to be interpreted with caution, as very high heterogeneity was detected in this outcome (I^2 = 85%). One factor may relate to the scaling factors used in estimating the standard deviations of monthly exacerbation rates, which may have led to over-precision in the estimates from each study. For this reason, monthly exacerbation results may be less reliable than those pertaining to the outcome above that assessed whether participants had experienced an exacerbation during the study period. We were unable to include in our review exacerbation data from a large American study (Petty 1990). The paper reported no significant differences in exacerbation rates between groups treated with iodinated glycerol and those given placebo, but no data were available on this outcome.

Parr 1987 reported no measurements of error for their exacerbation rate. Owing to the large number of included 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, no change in effect size is seen. 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 reported for mucolytics, no significant reduction in exacerbation rates was observed with the thiol donor N-isobutyrylcysteine (NIC). Addition of NIC to the main analysis resulted in no change in overall effect size.

A significant difference in this outcome was reported by study duration - those studies lasting 12 months or longer had a smaller effect than average (0.02 fewer per month, 95% CI -0.02 to -0.01), and those completed within three months showed a greater effect (test for subgroup differences: Chi^2 = 60.95, df = 2; P value

< 0.00001; Analysis 1.8).
Effect size did not vary by type of mucolytic or dose (Analysis 1.5), by lung function at baseline (Analysis 1.6) or by whether participants had a history of exacerbations (Analysis 1.10).

Exacerbations in patients not given inhaled corticosteroids (ICS)

A meta-analysis of earlier studies, which were defined or stratified by non-use of concomitant ICS (Decramer 2005; Malerba 2004; Schermer 2009; see Analysis 1.7), found no significant differences in exacerbation rates between those treated with mucolytics and those given placebo (MD 0.02; 95% CI -0.01 to 0.04). One recent study (Zheng 2014) noted no significant interaction between ICS use and treatment effect (P value = 0.27). Another study (Roy 2014) excluded participants given ICS but provided no reportable data on exacerbations.

Time to first exacerbation

Sufficient data with which to perform a meta-analysis are not yet available for this clinically relevant outcome. Post hoc analysis of the EQUALIFE study (Ballabio 2008) revealed that participants given erdosteine had a significantly longer time until their first exacerbation compared with those given 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, participants with chronic obstructive pulmonary disease (COPD) treated with N-acetylcysteine (NAC) had a mean of 139 days (SD 68) to first exacerbation versus 108 (79) days for those given placebo (P value < 0.05). More recently, Zheng 2014 reported no differences between time to first exacerbation in NAC- or control-treated groups, but time to second and third exacerbations was shorter in the control group.

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

Thirteen studies showed a significant reduction of 0.43 days of disability per participant per month with mucolytic therapy (95% CI -0.56 to -0.30; Analysis 1.11) compared with placebo. This finding was associated with a high level of heterogeneity (I^2 = 61%).
Moretti 2004 did not report total 'sick days'; however, investigators did report the numbers 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.
In the three studies that reported it, a mean reduction of 0.53 days on antibiotics per participant per month was observed (95% CI -0.76 to -0.31; Analysis 1.12). These were older studies that included participants with chronic bronchitis. In the study of Meister 1999, 6/31 (52%) participants in the myrtol group with exacerbations needed antibiotics, compared with 30/49 (61%) in the placebo group. Courses of antibiotics were longer in the placebo group. The percentage of participants who needed antibiotics for longer than seven days was 37% in the myrtol group and 77% in the placebo group. Malerba 2004 reported no differences between ambroxol and placebo in terms of duration of courses of antibiotic treatment, working days lost or number of days of hospitalisation (no data given). Moretti 2007 used post hoc analyses to report that compared with placebo, erdosteine use was associated with relatively fewer antibiotic courses (32%) and shorter durations of treatment (15%). The mean number of antibiotic courses per participant treated with erdosteine was also lower than for those given placebo (0.5 (SD 0.7) vs 0.7 (SD 0.7); P value = 0.045).

Health-related quality of life

Although many studies reported participant and/or physician global assessments of well-being, only eight used validated tools to evaluate health-related quality of life among participants with COPD. In seven studies (De Backer 2013; Decramer 2005; Moretti 2004; Tse 2013; Worth 2009; Zheng 2008; Zheng 2014), investigators used the St George's Respiratory Questionnaire (SGRQ; Jones 1992), and in one study (Schermer 2009), researchers used the Chronic Respiratory Questionnaire (CRQ; Guyatt 1987).
The SGRQ total score is derived from scores on three subscales - symptoms, activities and impacts - to yield a score out of 100 (Jones 1992). A well person has respiratory disease scores around 7 (Jones 1992). Lower scores indicate better quality of life.
When they were reported, we combined total scores on the SGRQ at the end of the treatment period (Analysis 1.13). This revealed a small, statistically significant effect in favour of mucolytics when a fixed-effect model was used (MD -2.60, 95% CI -4.29 to -0.9) and when a random-effects model was applied (MD -2.64, 95% CI -5.21 to -0.08). Considerable heterogeneity among studies was apparent (I^2 = 51%). This effect does not meet the minimum clinically important difference of -4 units on the SGRQ (Jones 2005). However it is not possible to assess the impact of mucolytics at a population level without performing a responder analysis, and the size of the treatment effect was similar to that of tiotropium in comparison with placebo (Karner 2014).
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 treatment and placebo groups showed significantly improved scores on both scales, with no significant differences between groups (-3.76 units on NAC and -4.95 units on placebo; difference between groups 1.18; P value = 0.358, as reported in the text of the paper). In the second year, this improvement tailed off again, with no differences noted between treatment groups. More participants given 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 study authors as obtained from the mixed-effects model used in this study. In Zheng 2008, baseline SGRQ scores were well matched among groups. After 12 months of treatment, changes in SGRQ total scores from baseline amounted to -4.06 units in the carbocysteine group and -0.05 in the placebo group, but these values did not represent a statistically significant difference between groups (P value = 0.13). A very large difference in SGRQ symptom domain results between the carbocysteine group (-11.34 units) and the placebo group (-3.54 units; P value = 0.004) remains unexplained. Results from the single measurement obtained at one year in this study contrast with multiple measurements taken in Decramer 2005, by which no significant differences in symptom scores between NAC and placebo were found over time.

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 value = 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 Short Form (SF)-36 and the SGRQ. The erdosteine-treated group showed significant improvement in all domains of the SGRQ, as well as in total score, and no differences between treated and placebo groups were reported. Data were not suitable for inclusion in Analysis 1.13.

In the three-year study of NAC versus placebo (Schermer 2009), the CRQ was used. Groups were well matched at baseline, with evident improvement 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, no significant differences in CRQ total scores were reported between groups (P value = 0.306).

Thus, considerable variation can be seen in evidence related to health-related quality of life, and we are not able to assess whether mucolytics had a clinically important effect on this outcome.

Hospitalisation

Comparative data were provided by four studies (Decramer 2005; Moretti 2004; Tse 2013; Zheng 2014). The odds ratio (OR) for hospitalisation with mucolytic treatment compared with placebo was 0.68 (95% CI 0.52 to 0.89; Analysis 1.14); however, considerable heterogeneity in this result was observed (I^2 = 58%), and benefit was seen only in the two smaller studies (Moretti 2004; Tse 2013). Malerba 2004 reported no significant differences in hospitalisation rates but did not provide data. Bachh 2007 reported a significant reduction (P value < 0.05) in hospitalisations when four months of NAC treatment was provided, with 55 hospitalisations reported for 50 participants in the control group but for only 37 of 50 in the treated group. As presented, these data cannot be included in the meta-analysis because the number of events exceeds the number of participants in the control group. If a conservative estimate of hospitalisations in the control group is made by entering them as 50 (not 55), the beneficial effect of mucolytics on hospitalisation is greater (OR 0.62, 95% CI 0.48 to 0.80) but heterogeneity is increased (I^2 = 76%). Mucolytics may be associated with a small decrease in hospitalisations.

Days in hospital were reported by Moretti 2004. In this study, participants taking erdosteine spent 70 days in hospital, compared with 163 days for the placebo group (P value = 0.04). This represented a mean of 1.1 days per treated participant compared with 2.7 days per control participant.

Lung function

All studies that reported a simple measure of airways obstruction are combined in the outcome of forced expiratory volume in one second (FEV_1) or %FEV_1 or peak expiratory flow rate (PEFR), which shows a significant difference at the end of treatment between mucolytic-treated and placebo-treated participants favouring mucolytic therapy (standardised mean difference (SMD) 0.09, 95% CI 0.02 to 0.16; Analysis 1.15). Significant heterogeneity is apparent in this result (I^2 = 64%), so it must be interpreted with caution. If only double-blind studies are included, the effect size is a little smaller (SMD 0.08, 95% confidence interval (CI) 0.00 to 0.15).

This analysis includes data from the Moretti 2004 study, which reported a significant difference (> 300 mL) between mucolytic and placebo groups at the end of the study; 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, a significant difference between groups is no longer observed and heterogeneity is removed.

Ten studies reported a small but significant 50 mL difference in forced vital capacity (FVC) at the end of the study period between participants treated with mucolytics and those given placebo (Analysis 1.16) (MD 0.05, 95% CI 0.03 to 0.08).

In contrast, the BRONCUS study of Decramer 2005 found no differences between NAC-treated and placebo-treated groups over three years in terms of decline in FEV_1, FVC or diffusing capacity of the lung for carbon monoxide (DLCO). FEV_1 declined by 54 mL and 47 mL, respectively, in the two groups. Study authors reported 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 value < 0.01) for NAC-treated participants, whereas for those treated with placebo, a decrease of only 0.008 L was reported. Moreover, the other three-year study (Schermer 2009) found no differences between groups in lung function at the end of the study. In the NAC-treated group, FEV_1 declined by 64 mL, and in the placebo group, by 60 mL. The decline in FVC was 79 mL and 65 mL, respectively.

In another large, well-conducted RCT (Zheng 2008), mean post-bronchodilator FEV_1 and oxygen saturations at the end of the study were not significantly different between those in 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 the HIACE study of Tse 2013, a significantly higher mean FEV_1 was reported for the NAC group at the end of the study, but this reflected differences at baseline, with no significant differences in the amount of change reported between groups. On the other hand, researchers reported significantly greater changes in the NAC group than in the placebo group for two measures of small airways function: forced expiratory flow at 25% to 50% (FEF_{25-50}) (P value = 0.037) and forced oscillation technique (FOT) (P value = 0.04),as well as for airways resistance (P value = 0.01).

Recently, a cross-over study (De Backer 2013) examined the effects of high-dose NAC given for three months on the geometry of airways in 12 participants. For most participants, no significant changes in spirometry or airways resistance were reported; however, two participants showed larger changes, raising the possibility of a responder phenotype.

In summary, it is likely that if mucolytics affect disease progression in chronic bronchitis or COPD, changes are very small and are confined to as-yet small and undefined subgroups.

Adverse effects

The meta-analysis of total numbers of adverse effects marginally favours mucolytic treatment, but with some heterogeneity (Peto OR 0.88, 95% CI 0.78 to 1.00; I^2 = 37%; Analysis 1.17). If a random-effects model is used, this finding is not statistically significant (OR 0.86, 95% CI 0.72 to 1.03). Moreover, this analysis does not include data from several large studies. Parr 1987 reported 1263 events in 258 participants in the mucolytics group (mean 4.9 per participant) and 1202 events in 268 participants in the placebo group (mean 4.5 per participant). Decramer 2005 reported 1428 events in 256 participants in the mucolytics group (mean 5.58 per participant) and 1381 events among 267 participants in the placebo group (mean 5.17 per participant). None were thought to be drug-related. Similar numbers in each group were admitted to hospital (55 and 69, respectively). Another study (Rasmussen 1988) described 54 events in 59 participants in the mucolytic group and 66 events in 57 participants in the placebo group. Meister 1999 reported 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 event rates exceeded numbers included in the treatment groups. Malerba 2004 also reported no greater risk of events and no greater severity of events with mucolytic treatment compared with placebo.

In summary, clinical studies have reported probably no difference between mucolytic and placebo treatments in terms of the total numbers of adverse effects that they cause.

Deaths

Eight studies reported on numbers of deaths in mucolytic-treated and placebo groups, revealing no significant differences (Peto OR 1.03, 95% CI 0.52 to 2.03; Analysis 1.18). As no deaths were reported in either group in Zheng 2008, this information could not be incorporated into the meta-analysis.

DISCUSSION

Summary of main results

The previous update of this review was performed in 2012 (Poole 2012). Since that time, a further four studies that were eligible for inclusion have been conducted (De Backer 2013; Roy 2014; Tse 2013; Zheng 2014). Owing to interest in the efficacy of higher and longer doses of NAC, we have included subgroup analyses of the effects of mucolytics in studies of 12 months or longer (Analysis 1.8) and the effects of N-acetylcysteine (NAC) at higher doses (1200 or 1800 mg per day; Analysis 1.5).

The present update strengthens findings from our previous reviews indicating that participants given a mucolytic agent for an average of 10 months are more likely to be exacerbation-free during that time (odds ratio (OR) 1.75). For one participant to be exacerbation-free, eight need to be treated for at least 10 months. The improvement in total number of exacerbations per participant per month is, at best, 0.3, which is about one fewer exacerbation every three years. Mucolytics may be associated with a small decrease in hospitalisations. With the addition of newer studies, certainty that mucolytics do not have an effect on lung function decline, mortality or adverse effects is increasing. The impact on quality of life as measured by the total St George Respiratory Questionnaire (SGRQ) score is smaller than the clinical minimally important difference of 4 units, but we cannot rule out a population benefit, as we do not have a responder analysis.

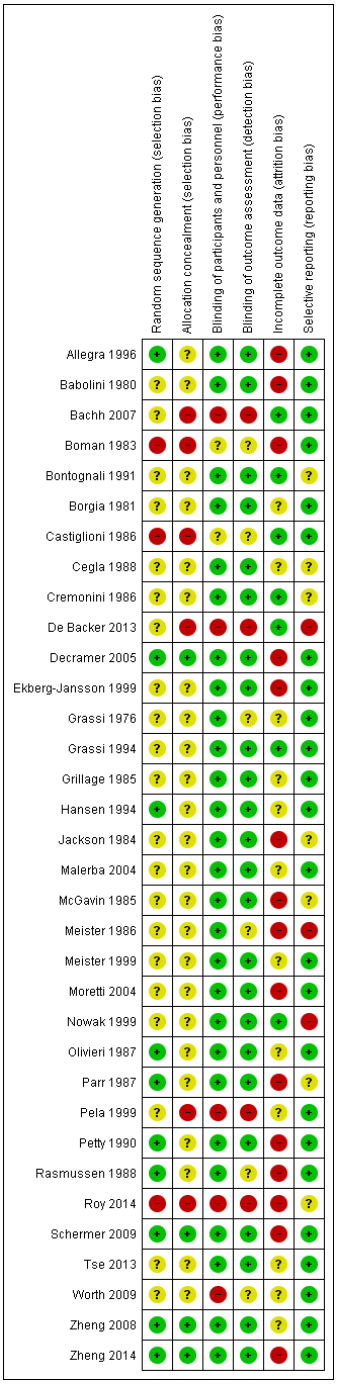
For many outcomes - primary and secondary - significant heterogeneity has been noted among studies; therefore the results do need to be interpreted with particular caution. The only outcomes for which heterogeneity among trials was not significant were days on antibiotics, forced vital capacity (FVC) and death during the study period. To explore causes of heterogeneity for the primary outcome of exacerbations, we performed subgroup analyses according to study date, baseline forced expiratory volume in one second (FEV_1) (as % predicted), type of mucolytic, dose of mucolytic, duration of therapy, whether participants were included because they had a history of exacerbations, whether concomitant inhaled steroids were used and the country in which the study was conducted. Heterogeneity was generally less among later trials, those with winter treatment only, those with no inhaled corticosteroids (ICS) and those with NAC 1200 mg/d.

The tendency for participants given mucolytics to have fewer exacerbations or to be more likely to be exacerbation-free was seen

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

However, when we performed a post hoc investigation comparing more recent study results versus those from previous decades, we found a clear reduction in the effects of treatment in more recent studies (see Figure 4; I^2= 93.3% between subgroups). Although all studies included in this analysis were placebo-controlled, and most were double-blind, the older studies were more difficult to judge in terms of bias (see Figure 6), and this may have led to an overestimation of treatment effect. Therefore we have a reduced level of confidence in the overall treatment effect estimate indicating that eight additional participants would need to be treated with mucolytics over 10 months to keep an additional participant free from exacerbations. We found no significant differences in adverse events or mortality (see Summary of findings for the main comparison).

Figure 6. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



On the other hand, internal consistency is evident in the findings, in that the small effect on exacerbation rate is accompanied by a greater likelihood that patients would be exacerbation-free and that exacerbations would be less prolonged.

To provide some context for the interpretation of findings in this review, the ISOLDE trial, which treated participants with moderately severe chronic obstructive pulmonary disease (COPD) 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 - for an absolute reduction of 0.33 exacerbations per year, or 25% (Burge 2000). In other studies, long-acting beta-agonists, long-acting muscarinic antagonists, phosphodiesterase $(PDE)_4$ inhibitors and azithromycin have been shown to significantly reduce exacerbation frequency.

Theoretical reasons have been proposed to explain why mucolytics may modify disease in ways other than by reducing exacerbations (i.e. through antioxidant and thiol donor effects). More recent studies have sought to explore whether the decline in FEV_1 over time is changed by mucolytics. NAC has been used at higher doses or for longer durations without providing additional benefits. The reduction in exacerbation rates seen with NAC was virtually identical to that observed with other mucolytics examined as a group. The mechanisms responsible for the benefits of mucolytic treatment on exacerbation rates and days of disability cannot be identified by this review. However, lack of effect of 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 benefit presented by earlier studies, none of the large studies (BRONCUS study, PEACE study, COOPT, HIACE, PANTHEON) showed significant slowing of the decline in FEV_1 with mucolytic treatment. On the other hand, no evidence suggests that mucolytics are unsafe, and findings indicate that 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 substantively six times. Over time, with a steady increase in the numbers of studies published, even though a significant treatment effect of mucolytics on exacerbations has always been observed, the size of this effect has decreased by almost 50% from that described in the original report. This trend may be observed in Figure 4, where studies have been ordered by year of publication and separated by decade of publication.

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

Improved study design, execution and reporting over the years

Confidence intervals are narrower, and consequently greater weight is afforded to more recent studies. The forest plot in Figure 4 has been arranged by date and shows this trend. Part of the explanation is that more recent studies, on average, have been larger than earlier ones. Another consideration is that publication bias may have influenced reporting of results of earlier trials. This is suggested by an asymmetrical funnel plot in Analysis 1.1 (Figure 5). We have persisted with using the more conservative fixed-effect model, which gives greater weight 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 (mean difference (MD) -0.07, 95% confidence interval (CI) -0.09 to -0.05), but the degree of heterogeneity remains.

Furthermore, 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 needed only to have symptoms of chronic bronchitis. Additionally, later studies have been longer so may be more robust in ascertaining mean exacerbation rates. Finally, as was mentioned previously, older studies may be at greater risk of selection bias, which may have inflated estimates of the treatment effect.

Recent studies have tended to be longer. Analysis 1.8 shows an inverse relationship between effect size and study duration. Although this may represent regression to the mean, an element of 'immortal time bias' may have been introduced, although exposure time was longer in the intervention group (through fewer dropouts) than in the placebo group (more dropouts). This would allow more exacerbations to be recorded for those remaining in the study, hence diluting any treatment effect.

Improved COPD care

Comprehensive management of COPD includes support for smoking cessation, vaccination, pulmonary rehabilitation and use of inhaled corticosteroids, long-acting beta-agonists and anticholinergic agents (GOLD 2015), each of which may impact exacerbation frequency or severity.

Lower exacerbation rates would allow less room for improvement with mucolytics. In support of this, lower monthly exacerbation rates have been reported in the control groups of studies reported since 2000 (0.12 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 1.4). On the other hand, no trend has been seen in the likelihood that participants in control groups would be exacerbation-free: 38% in pre-1990 studies, 52% between 1990 and 2000 and 36% since 2000 (derived from Analysis 1.2). Taken together, these findings suggest

that over a third of study participants with COPD will have an exacerbation. In more recent studies, those who do exacerbate have fewer exacerbations, possibly because of improved COPD care generally.

Inhaled corticosteroids (ICS) have been available for asthma since the late 1970s, but it is unlikely that they were used by participants with chronic bronchitis in trials before 1990. In most of the other studies, ICS treatment was allowed. Data from five studies have addressed the relative effects of mucolytics and ICS. Malerba 2004 specifically excluded those taking ICS, and Decramer 2005 reported results for the subgroup not given ICS. Based on the report of average lung function, participants in these two studies had relatively mild COPD. The weighted annual event rate in relevant placebo groups from these two studies was 1.04, revealing a 17% reduction in exacerbations with mucolytics. The effect of mucolytics among non-ICS-treated participants in these two studies showed an MD of around -0.21 exacerbations per year, or -0.02 per month compared with placebo. This is about half that seen when all mucolytic studies are combined. It is difficult to know the meaning 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 participants were taking ICS (compared with 70% in Decramer 2005), but investigators found no differences in effects of carbocysteine between those taking and those not taking concomitant ICS. They did suggest that doses of ICS would have been low in this small group of participants, making findings not necessarily at odds with those of 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 with placebo, but this finding did not reach statistical significance (P value = 0.054). Investigators also found the exacerbation rate to be 1.30 times higher with fluticasone (P value = 0.095), suggesting that effect sizes were similar between NAC and fluticasone. As the result of methodological issues with this study, including high dropout rates and skewed exacerbation rates, it is difficult to be certain about this. In Zheng 2014, 44% of participants were taking ICS. These study authors found that use of ICS was the only co-variate that affected the exacerbation rate in study participants, but they noted no interaction between ICS use and effects of mucolytics (P value = 0.27).

Quality of the evidence

Although almost all of the trials included in this review were double-blind, only four studies had clearly concealed allocation (Decramer 2005; Schermer 2009; Zheng 2008; Zheng 2014). In combination with time trends (less optimistic results in more recent trials), the possibility of publication bias seen in the funnel plot (Figure 5), and high and unbalanced dropout rates in some of the longer trials (e.g. Decramer 2005), this indicates that the overall risk that bias inflated these trial results is high. Thus further research is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate towards the null effect.

Potential biases in the review process

The subgroup analysis by decade of publication is post hoc for updates from 2012 onward; therefore we have not assessed the likelihood that differences between subgroups have arisen by chance. On the other hand, consistency in the findings of this review has been seen over its multiple iterations since 1997, despite the addition of new outcomes, analyses and review authors.

In a few analyses, we have imputed standard deviations. When this has been done, it has been done conservatively and in accordance with accepted practices. This could have narrowed the confidence intervals for individual studies, thus increasing heterogeneity. Furthermore, the approach that 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 the use of a consistent approach, slight rounding errors may have been 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, two other systematic reviews of the effects of NAC in chronic bronchitis have been reported. Our results are consistent with these findings. The larger of these reviews included 11 randomised controlled trials (RCTs) (Stey 2000). Overall, individuals treated with NAC were more likely to remain exacerbation-free (OR 1.56, 95% CI 1.37 to 1.77), with an NNTB of 6 (95% CI 5 to 9). Participants were more likely to report 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 Stey 2000 and this Cochrane review and confirmed a significant effect on exacerbations (standardised mean difference (SMD) -1.37, 95% CI -1.5 to -1.25) (Grandjean 2000).

In a recent guideline on treatments to prevent COPD exacerbations, NAC was suggested for patients with moderate or severe COPD and a history of two or more exacerbations in the previous two years (evidence grade 2B - weak recommendation, moderate-quality evidence; Criner 2015). Furthermore, carbocysteine was suggested (ungraded consensus-based statement) for patients still having exacerbations in spite of maximal therapy provided to reduce exacerbations. The most recent version of global COPD

guidelines (GOLD 2015) states that NAC may have a role in the treatment of patients with recurrent exacerbations (evidence grade B - moderate-quality evidence), and carbocysteine or NAC may reduce exacerbations in patients not taking inhaled steroids (grade B).

Our findings suggest that the addition of a mucolytic may have a small beneficial effect on both the likelihood of any exacerbation and the total number of exacerbations. Differences among mucolytic agents, or among those with greater doses, have not been found, although this would need to be tested in head-to-head comparisons.

The analyses in this review suggest that mucolytics might, in addition, have an effect on duration and severity of exacerbations that do occur, and on the likelihood of taking antibiotics. Data from four 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 most costs associated with more severe disease are incurred. Few other pharmacological treatments have been shown to reduce hospitalisation: An immunomodulatory agent OM-85 BV, or Broncho-Vaxom (Collet 1997), was shown to reduce the number of hospital admissions in COPD, even though it did not affect the number of exacerbations.

Researchers (Grandjean 2000a) performed a retrospective cost-effectiveness analysis of NAC in chronic bronchitis that was based on direct costs of NAC treatment, management of an acute exacerbation and indirect costs of sick leave. Results suggested that costs of treatment and non-treatment were equal at the point of a reduction of 0.6 exacerbations per six-month period. In our review, a reduction of about 0.18 per six-month period suggested 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 would cost INR 200 (USD 4). ICS are also expensive. As the burden of COPD over coming decades is going to disproportionately affect developing nations, the relative costs of each strategy are important to determine.

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. The reduction is at most one fewer exacerbation every three years. One person in eight may avoid having an exacerbation, provided all take treatment every day for an average of 10 months. Mucolytics have not been shown to slow the decline in lung function, and it is uncertain whether they improve quality of life or hospitalisations.

As reduction in exacerbations seems the main potential benefit, mucolytics might be considered (1) a treatment option for patients with frequent exacerbations who cannot take other therapies such as inhaled corticosteroids or long-acting bronchodilators, which have a stronger evidence base for their effectiveness; or (2) add-on treatment once all other therapies to reduce exacerbations have been utilised,

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 despite maximal therapy to reduce acute exacerbations of COPD.

Studies should stratify participants by (1) the new GOLD criteria (A-D; GOLD 2015), which incorporate symptoms and exacerbations, as well as spirometry; (2) use of concomitant medications (such as ICS, long-acting bronchodilators or macrolide antibiotics).

Outcomes of studies should include hospitalisations (COPD and all-cause), mortality (COPD and all-cause), numbers of days sick with exacerbations and a validated measure of quality of life. A responder analysis for quality of life would add valuable information on the population effects of treatment.

ACKNOWLEDGEMENTS

This review is dedicated to the memory of Professor Peter Black, FRACP, who died in 2010. Peter made significant and broad contributions to asthma and COPD research, including work as a reviewer and editor for the Cochrane Airways Group.

We would like to acknowledge the contributions of the following.

- Peter Black, who was the co-author of the first four versions of this review.
- Emma Welsh, Peter Gibson, Paul Jones and Toby Lasserson of the Cochrane Airways Group for editorial support.
- Emma Jackson, Anna Bara, Karen Blackhall and Liz Stovold of the Cochrane Airways Group for searching and retrieving full-text articles.
- Translators Ms Sharon Kramer, Dr Silvana Campanella, Dr Ruth Black, Dr Klaus Lehnert, Ms Daniela Screnci and Mr Toby Lasserson.

• Professor Marc Decramer, who provided information on SGRQ scores from Decramer 2005.

• Dr Zheng, who gave us more information on Zheng 2008 and Tatsumi 2007a, as well as the appendix to Zheng 2014. For the latter study, Dr Zheng kindly provided further data on exacerbation rate, SGRQ and spirometry.

• Dompe Farmaceutici (Allegra 1996), which provided us with further data.

• Zambon Group for providing the study Meister 1986, and for further information on Nowak 1999.

• Douglas Pharmaceuticals and G. Pohl Boskamp for information on Meister 1999.

• Other study authors and companies that took the trouble to write back, even though they could not provide further data (Dr Petty, Dr Boman, Novartis Pharmaceuticals).

REFERENCES

References to studies included in this review

Allegra 1996 *{published and unpublished data}*
Allegra L, Cordaro CI, Grassi C. Prevention of acute exacerbations of chronic obstructive bronchitis with carbocysteine lysine salt monohydrate: a multicenter, double-blind, placebo-controlled trial. *Respiration* 1996;**63**: 174–80.

Babolini 1980 *{published data only}*
Multicenter Study Group. Long-term oral acetylcysteine in chronic bronchitis. A double-blind controlled study. *European Journal of Respiratory Disease* 1980;**61**(111 Suppl): 93–108.

Bachh 2007 *{published data only}*
Bachh AA, Shah NN, Bhargava R, Ahmad Z, Pandey DK, Dar KA. Effect of oral N-acetylcysteine in COPD - a randomised controlled trial. *JK-Practitioner* 2007;**14**(1): 12–6.

Boman 1983 *{published data only}*
Boman G, Backer U, Larsson S, Melander B, Wahlander L. Oral acetylcysteine reduces exacerbation rate in chronic bronchitis; report of a trial organized by the Swedish Society for Pulmonary Diseases. *European Journal of Respiratory Disease* 1983;**64**:405–15.

Bontognali 1991 *{published data only}*
Bontognali E. Clinical effectiveness and tolerance of cithiolone in the prophylaxis of acute infective exacerbations in patients suffering from chronic bronchitis. *Acta Therapeutica* 1991;**17**:155–62.

Borgia 1981 *{published data only}*
Borgia M, Sepe N, Ori-Belometti M, Borgia R. Comparison between acetylcysteine and placebo in the long term treatment of chronic bronchitis [Confronto tra acetilcisteina e placebo nel trattamento a lungo termine della bronchite cronica]. *Gazzetta Medica Italiana* 1981;**140**:467–72.

Castiglioni 1986 *{published data only}*
Castiglioni CL, Gramolini C. Effect of long-term treatment with sobrerol on the exacerbations of chronic bronchitis. *Respiration* 1986;**50**:202–17.

Cegla 1988 *{published data only}*
Cegla UH. Long-term treatment of chronic bronchitis for two years with ambroxol (Mucosolvan) retard capsules. Results of a double blind trial including 180 patients [Langzeittherapie uber 2 Jahre mit Ambroxol (Mucosolvan) Retardkapseln bei Patienten mit chronischer Bronchitis. Ergebnisse einer Doppelblindstudie an 180 Patienten]. *Praxis Klinik der Pneumologie* 1988;**42**:715–21.

Cremonini 1986 *{published data only}*
Cremonini C, Spada E, Cellini F, Cioni R, Giovannini M, Perri G, et al. I farmaci attivi sul muco nel trattamento di fondo della bronchite cronica [Pharmacotherapy which acts on mucus in long–term treatment of chronic bronchitis]. *La Clinica Terapeutica* 1986;**116**:121–9.

De Backer 2013 *{published data only}*
De Backer J, Vos W, Van Holsbeke C, Vinchurkar S, Claes R, Parizel P, et al. Double blind, randomized, two-way crossover, pilot study to assess the effect of high dose N-acetylcysteine on airway geometry, inflammation and oxidative stress in COPD patients using functional respiratory imaging. American Journal of Respiratory and Critical Care Medicine May 17-22. 2013.
* De Backer J, Vos W, Van Holsbeke C, Vinchurkar S, Claes R, Parizel PM, et al. Effect of high-dose N-acetylcysteine on airway geometry, inflammation, and oxidative stress in COPD patients. *International Journal of Chronic Obstructive Pulmonary Disease* 2013;**8**:569–79.

Decramer 2005 *{published data only}*
Decramer M, Rutten-van Molken M, Dekhuijzen PN, Troosters T, van Herwaarden C, Pellegrino R, et al. Effects of N-acetylcysteine on outcomes in chronic obstructive pulmonary disease (Bronchitis Randomized on NAC Cost-Utility Study, BRONCUS): a randomised placebo-controlled trial. *Lancet* 2005;**365**(9470):1552–60.

Ekberg-Jansson 1999 *{published data only}*
Ekberg-Jansson A, Larson M, MacNee W, Tunek A, Wahlgren L, Wouters EFM, et al. N isobutyrylcysteine, a donor of systemic thiols, does not reduce the exacerbation rate in chronic bronchitis. *European Respiratory Journal* 1999;**13**(4):829–34.

Grassi 1976 *{published data only}*
Grassi C, Morandini GC. A controlled trial of intermittent oral acetylcysteine in the long-term treatment of chronic bronchitis. *European Journal of Clinical Pharmacology* 1976; **9**:393–6.

Grassi 1994 *{published data only}*
Grassi C, Casali L, Ciaccia A, et al. Terapia intervallare con l'associazione carbocisteina-sobrerolo nella profilassi delle riacutizzazioni della bronchite cronica. *Italian Journal of Chest Disease* 1994;**48**:17–26.

Grillage 1985 *{published data only}*
Grillage M, Barnard-Jones K. Long-term oral carbocisteine therapy in patients with chronic bronchitis. A double blind trial with placebo control. *British Journal of Clinical Practice* 1985;**39**(10):395–8.

Hansen 1994 *{published data only}*
Hansen NC, Skriver A, Brorsen-Riis L, Balsløv S, Evald T, Maltbaek N, et al. Orally administered N-acetylcysteine may improve general well-being in patients with mild chronic bronchitis. *Respiratory Medicine* 1994;**88**:531–5.

Jackson 1984 *{published data only}*
Jackson IM, Barnes J, Cooksey P. Efficacy and tolerability of oral acetylcysteine (fabrol) in chronic bronchitis: a double-blind placebo controlled trial. *Journal of International Medical Research* 1984;**12**:198–206.

Malerba 2004 *{published data only}*
Malerba M, Ponticello A, Radaeli A, Bensi G, Grassi V. Effect of twelve-months therapy with oral ambroxol in preventing exacerbations in patients with COPD. Double-blind, randomized, multi-center, placebo-controlled study (the AMETHIST trial). *Pulmonary Pharmacology & Therapeutics* 2004;**17**(1):27–34.

McGavin 1985 *{published data only}*
British Thoracic Society Research Committee. Oral N-acetylcysteine and exacerbation rates in patients with chronic bronchitis and severe airways obstruction. *Thorax* 1985;**40**(11):832–5.

Meister 1986 *{unpublished data only}*
Meister R. Long-term therapy with acetylcysteine retard tablets in patients with chronic bronchitis: a double-blind, placebo controlled study. Unpublished source 1986.

Meister 1999 *{published data only}*
* Meister R, Wittig T, Beuscher N, de Mey C. Efficacy and tolerability of myrtol standardized in long-term treatment of chronic bronchitis. A double-blind, placebo-controlled study. Study Group Investigators. *Arzneimittelforschung* 1999;**49**(4):351–8.

Moretti 2004 *{published data only}*
* Moretti M, Bottrighi P, Dallari R, Da Porto R, Dolcetti A, Grandi P, et al. The effect of long-term treatment with erdosteine on chronic obstructive pulmonary disease: the EQUALIFE study. *Drugs Under Experimental & Clinical Research* 2004;**30**(4):143–52.

Nowak 1999 *{published data only}*
Nowak D, Carati L, Pirozynski M. Long-term administration of N-acetylcysteine reduces the number of acute exacerbation episodes in subjects with chronic obstructive pulmonary disease:report of the BREATHE study. *European Respiratory Journal* 1999;**14 Suppl**: 381S–2S.

Olivieri 1987 *{published data only}*
Olivieri D, Zavattini G, Tomasini G, Daniotti S, Bonsignore G, Ferrara G, et al. Ambroxol for the prevention of chronic bronchitis exacerbations: long-term multicenter trial. *Respiration* 1987;**51 Suppl 1**:42–51.

Parr 1987 *{published data only}*
Parr GD, Huitson A. Oral fabrol (oral n-acetyl-cysteine) in chronic bronchitis. *British Journal of Diseases of the Chest* 1987;**81**(4):341–8.

Pela 1999 *{published data only}*
Pela R, Calcagni AM, Subiaco S, Isidori P, Tubaldi A, Sanguinetti CM. N-acetylcysteine reduces the exacerbation rate in patients with moderate to severe COPD. *Respiration* 1999;**66**(6):495–500.

Petty 1990 *{published data only}*
Morgan EJ, Petty TL. Summary of the national mucolytic study. *Chest* 1990;**97**(Suppl):24S–7S.
* Petty TL. The national mucolytic study: results of a randomized, double-blind, placebo-controlled study of iodinated glycerol in chronic obstructive bronchitis. *Chest* 1990;**97**(1):75–83.

Rasmussen 1988 *{published data only}*
Rasmussen JB, Glennow C. Reduction in days of illness after long-term treatment with N-acetylcysteine controlled-release tablets in patients with chronic bronchitis. *European Respiratory Journal* 1988;**1**:351–5.

Roy 2014 *{published data only}*
Roy P, Haran A, Srinivas BN. Role of n-acetylcysteine as an adjuvant to mainstay bronchodilator therapy in chronic obstructive pulmonary disease. Indian Journal of Pharmacology Conference Publication. 2013; Vol. 45: S107.
* Roy P, Haran A, Srinivas BN, Mjumdar P. Evaluation of effect of N-acetylcysteine as an adjuvant to mainstay bronchodilator therapy in mild to moderate cases of chronic obstructive pulmonary disease. *International Journal of Medical and Applied Sciences* 2014;**3**(1):95–105.

Schermer 2009 *{published data only}*
Chavannes N, Schermer T, Wouters EFM, Folgering H. Demographic and clinical determinants of response to N-acetylcysteine versus fluticasone in mild to moderate COPD in primary care: the COOPT study. European Respiratory Society 15th Annual Congress; 2005 Sep 17-20; Copenhagen. 2005; Vol. Abstract 1356:ERS05L1˙1255.
* Schermer T, Chavannes N, Dekhuijzen R, Wouters E, Muris J, Akkermans R, et al. Fluticasone and N-acetylcysteine in primary care patients with COPD or chronic bronchitis. *Respiratory Medicine* 2009;**103**:542–51.

Tse 2013 *{published data only}*
* Tse HN, Raiteri L, Wong KY, Yee KS, Ng LY, Wai KY, et al. High-dose N-acetylcysteine in stable COPD: the 1-year, double-blind, randomized, placebo-controlled HIACE study. *Chest* 2013;**144**:106–18.
Tse HN, Wong KY, Yee KS, Ng LY. The effect of high dose N-acetylcysteine (1200mg daily) on airway function and airway trapping in COPD patients: a double blinded

randomized placebo controlled trial. European Respiratory Society 22nd Annual Congress; 2012 Sep 1-5; Vienna. 2012; Vol. 40; Suppl 56.
Tse HN, Wong KY, Yee KS, Ng LY, Wai KY, Loo CK, et al. The effect of high dose N-acetylcysteine (600 mg twice daily) in patients with stable chronic obstructive pulmonary disease - a one-year, double blind, randomized, placebo-controlled trial. American Thoracic Society International Conference, May 17-22, Philadelphia. 2013.

Worth 2009 *{published data only}*
* Worth H, Schacher C, Dethlefsen U. Concomitant therapy with cineole (eucalyptole) reduces exacerbations in COPD: a placebo-controlled double-blind trial. *Respiratory Research* 2009;**10**(1):69.
Worth H, Schacher C, Dethlefsen U. Effects of concomitant therapy with Cineole (Eucalyptole) on exacerbation rate in COPD: a placebo-controlled double-blind trial. *In: European Respiratory Society 20th Annual Congress; 2010 Sep 18-22; Barcelona. Vol. P538. 2010.*

Zheng 2008 *{published data only}*
Zheng JP, Kang J, Huang SG, Chen P, Yao WZ, Yang L, et al. Effect of carbocisteine on acute exacerbations of chronic obstructive pulmonary disease (PEACE study): a randomised placebo-controlled trial. *Lancet* 2008;**371**(9629):2013–8.

Zheng 2014 *{published data only}*
Zheng JP, Wen FQ, Bai CX, Wan HY, Kang J, Chen P, et al. High-dose N-acetylcysteine in the prevention of COPD exacerbations: rationale and design of the PANTHEON study. *COPD: Journal of Chronic Obstructive Pulmonary Disease* 2013;**10**:164–71.
Zheng JP, Wen FQ, Bai CX, Wan HY, Kang J, Chen P, et al. High-dose N-acetylcysteine in the prevention of COPD exacerbations: results of the PANTHEON study. European Respiratory Society 23rd Annual Congress; 2013 Sep 7-11; Barcelona. 2013.
* Zheng JP, Wen FQ, Bai CX, Wan HY, Kang J, Chen P, et al. Twice daily N-acetylcysteine 600 mg for exacerbations of chronic obstructive pulmonary disease (PANTHEON): a randomised, double-blind placebo-controlled trial. *Lancet Respiratory Medicine* 2014;**2**:187–94.

References to studies excluded from this review

Baglioni 2001 *{published data only}*
Baglioni S, Tazza R, Rossi S, Eslami A, Ferranti P, Dottorini M. Effects of N-acetylcysteine treatment during long term oxygen therapy (LTOT) in COPD patients. An open parallel-group study. *European Respiratory Journal* 2001;**18**(33 Suppl):58S.

Cattaneo 2001 *{published data only}*
Cattaneo C. Neltenexine tablets in smoking and non-smoking patients with COPD. A double-blind, randomised, controlled study versus placebo. *Minerva Medica* 2001;**92**(4):277–84.

Christensen 1971 *{published data only}*
Andreasen T. Mucolytic treatment of chronic bronchitis during two winter periods. *Scandinavian Journal of Respiratory Disease* 1974;**90**:69–70.
Christensen SB, Kjer J, Ryskjaer S, Arseth-Hansen P, Christensen F. Mucolytic treatment of chronic bronchitis during two winter periods. *Scandinavian Journal of Respiratory Disease* 1971;**52**(1):48–57.

Edwards 1976 *{published data only}*
Edwards GF, Steel AE, Scott JK, Jordan JW. S-carboxymethylcysteine in the fluidification of sputum and treatment of chronic airway obstruction. *Chest* 1976;**70**(4):506–13.

Habich 1994 *{published data only}*
Habich G, Repges R. Chronic obstructive lung diseases: the efficacy of cineole [Cineol als medikation sinnvoll und bewart]. *Therapiewoche* 1994;**44**(6):356–65.

Kasielski 2001 *{published data only}*
Kasielski M, Nowak D. Long-term administration of N-acetylcysteine decreases hydrogen peroxide exhalation in subjects with chronic obstructive pulmonary disease. *Respiratory Medicine* 2001;**95**(6):448–56.

Lukas 2005 *{published data only}*
Lukas R, Scharling B, Schultze-Werninghaus G, Gillisen A. Administration of N-acetylcysteine and vitamin C to augment antioxidant properties in patients with chronic bronchitis. *Deutsche Medizinishe Wochenscrift* 2005;**130**:563–7.

Maesen 1980 *{published data only}*
Maesen FP, Brombacher PJ. Treatment of chronic bronchitis with oral acetylcysteine, a double-blind study. *European Journal of Respiratory Disease* 1980;**61**:110.

Michnar 1996 *{published data only}*
Michnar M, Milanowski J. Assessment of efficacy and tolerability of the oral treatment of ambrosol in patients with chronic bronchitis [Ocena kliniczna skutecznosci i tolerancji doustnego leczenia ambrosolem u chorych na przewlekle zapalenie oskrzeli]. *Pneumonologia i Alergologia Polska* 1996;**64**(Suppl 1):90–6.

Moretti 2011 *{unpublished data only}*
Moretti M, Ballabio M. Effect of erdosteine on airflow obstruction and symptom recovery in severe COPD exacerbations [Abstract]. European Respiratory Society 21st Annual Congress; 2011 Sep 24-28; Amsterdam. 2011; Vol. 38 (55):76s [P536].

Rubin 1996 *{published data only}*
Rubin BK, Ramirez O, Ohar JA. Iodinated glycerol has no effect on pulmonary function, symptom score, or sputum properties in patients with stable chronic bronchitis. *Chest* 1996;**109**(2):348–52.

Tatsumi 2007a *{published data only}*
Tatsumi K, Fukuchi Y. Carbocisteine improves quality of life in patients with chronic obstructive pulmonary disease. *Journal of the American Geriatrics Society* 2007;**55**(11):1884–5.

Tatsumi 2007b *{published data only}*

Tatsumi K, Fukuchi Y. Carbocisteine reduces the frequency of exacerbations in patients with COPD: findings from the PEACE study. Proceedings of American Thoracic Society International Conference, May 18-23, 2007, San Francisco, California, USA. 2007:C97.

Velazquez 2001 *{published data only}*

Velazquez A, Aguilar G, Sanchez C, Ochoa L, Sansores R, Remirez-Venegas A. The mucolytic effect on quality of life in patients with COPD. *American Journal of Respiratory and Critical Care Medicine* 2001;**163**(5 Suppl):A57.

Wilhelmi 2010 *{published data only}*

Wilhelmi E. Treatment of COPD: benefit of 1.8 cineole as co medication confirmed [Behandlung der COPD: nutzen voan 1.8–cineol als zusatztherapie bestatigt]. *Journal Pharmakol U Ther* 2010;**2**:554–5.

Additional references

Ballabio 2008

Ballabio M, Nicola M, Moretti M. Long-term use of antioxidant mucolytic erdosteine is especially beneficial in patient with more severe COPD. European Respiratory Society 18th Annual Congress; 2008 Oct 3-7; Berlin. 2008: abstract ERS08L1˙678.

Burge 2000

Burge PS, Calverley PM, Jones PW, Spencer S, Anderson JA, Maslen TK. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. *BMJ* 2000;**320**:1297–303.

Cates 2002

Cates CJ. Simpson's paradox and calculation of number needed to treat from meta-analysis. *BioMed Central* 2002; **BMC Medical Research Methodology 2**:1.

Collet 1997

Collet JP, Shapiro P, Ernst P, Renzi T, Ducruet T, Robinson A. Effects of an immunostimulating agent on acute exacerbations and hospitalizations in patients with chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine* 1997;**156**(6): 1719–24.

Criner 2015

Criner GJ, Bourbeau J, Diekemper RL, Ouellette DR, Goodridge D, Hernandez P, et al. Prevention of acute exacerbation of COPD: American College of Chest Physicians and Canadian Thoracic Society Guideline. *Chest* 2015;**147**(4):883–93.

GOLD 2015

Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD). http://www.goldcopd.org/ Accessed 2015.

Grandjean 2000

Grandjean EM, Berthet PH, Ruffman R, Leuenberger PH. Efficacy of oral long-term N-acetylcysteine in chronic bronchopulmonary disease: a meta-analysis of published double-blind, placebo-controlled clinical trials. *Clinical Therapeutics* 2000;**22**(2):209–20.

Grandjean 2000a

Grandjean EM, Berthet PH, Ruffman R, Leuenberger PH. Cost-effectiveness analysis of oral N-acetylcysteine as a preventive treatment in chronic bronchitis. *Pharmacology Research* 2000;**42**(1):39–50.

Guyatt 1987

Guyatt GH, Berman LB, Townsend M, Pugsley SO, Chambers LW. A measure of quality of life for clinical trials in chronic lung disease. *Thorax* 1987;**42**(10):773–88.

Jones 1992

Jones PW, Quirk FH, Baveystock CM, Littlejohns P. A self-complete measure of health status for chronic airflow limitation: the St. George's Respiratory Questionnaire. *American Review of Respiratory Disease* 1992;**145**(6):1321–7.

Jones 2005

Jones PW. St. George's Respiratory Questionnaire: MCID. *COPD* 2005;**2**(1):75–9.

Karner 2014

Karner C, Chong J, Poole P. Tiotropium versus placebo for chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews* 2014, Issue 7. [DOI: 10.1002/14651858.CD009285.pub3]

Moretti 2007

Moretti M, Nicola M. Prevention of COPD exacerbations and reduction of health care utilization with erdosteine. *European Respiratory Journal* 2007;**30**(Suppl 51):557s.

MRC 1965

Medical Research Council. Definition and classification of chronic bronchitis for clinical and epidemiological purposes. *Lancet* 1965;**286**(7416):775–81.

Rahman 2005

Rahman I. Oxidative stress in the pathogenesis of chronic obstructive pulmonary disease; cellular and molecular mechanisms. *Cell Biochemistry and Biophysics* 2005;**43**(1): 167–88.

Redline 1991

Redline S. Epidemiology of COPD. In: Cherniack N editor (s). *Chronic Obstructive Pulmonary Disease*. 1st Edition. Philadelphia: Saunders, 1991.

Stey 2000

Stey C, Steurer J, Bachmann S, Medici TC, Tramer MR. The effect of oral N-acetylcysteine in chronic bronchitis: a quantitative systematic review. *European Respiratory Journal* 2000;**16**(2):253–62.

References to other published versions of this review

Poole 1998

Poole PJ, Black PN. The effect of mucolytic agents on exacerbation frequency in chronic bronchitis. *Cochrane Database of Systematic Reviews* 1998, Issue 4. [DOI: 10.1002/14651858.CD001287]

Poole 1999

Poole PJ, Black PN. Mucolytic agents for chronic bronchitis. *Cochrane Database of Systematic Reviews* 1999, Issue 2. [DOI: 10.1002/14651858.CD001287]

Poole 2001

Poole PJ, Black PN. Oral mucolytic drugs for exacerbations of chronic obstructive pulmonary disease: systematic review. *BMJ* 2001;**322**:1271–4.

Poole 2006

Poole PJ, Black PN. Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews* 2006, Issue 3. [DOI: 10.1002/14651858.CD001287.pub2]

Poole 2012

Poole PJ, Black PN, Cates CJ. Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews* 2012, Issue 8. [DOI: 10.1002/14651858.CD001287]

* *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, multi-centre study, with 1 month run-in before randomisation. Duration 6 months. ITT and PP analysis
Participants	440 participants with chronic bronchitis (MRC). Age 20 to 70, FEV_1 40% to 70% and at least 2 exacerbations in previous 12 months Exclusions: neoplastic disease, TB, asthma or uncompensated liver, kidney or heart disease, pregnancy Other mucoactive and anticough agents, oral or inhaled corticosteroids not permitted Mean age 60 years, 75% had smoking history, FEV_1 2.12 (SD 0.6) litres, mean 2.7 (SD 1.3) exacerbations in past 12 months Dropouts: 89 (20%)
Interventions	3 treatment arms. Carbocysteine lysine salt monohydrate (SCMC-Lys) 2.7 g daily, placebo and SCMC-Lys 2.7 g daily alternating 1 week active, 1 week placebo. We assessed continuous vs 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. Requested data were provided by sponsoring company. Intention-to-treat analysis was used with an estimate of duration of treatment derived from the paper

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated, balanced per centre
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind. Matching placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	High risk	20% dropout rate (89/440)

Allegra 1996 (*Continued*)

Selective reporting (reporting bias)	Low risk	Reported main outcomes with ITT and PP analyses

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 L, FEV_1 40% to 70% predicted, 64.3% smokers. 249 dropouts. Baseline groups matched. Dropout groups matched	
Interventions	NAC 200 mg BD or placebo	
Outcomes	Exacerbations, symptom scores, global assessments by participants and physicians, adverse effects, days on antibiotics	
Notes	Italian. Same data also in Ferrari. SD calculated from graph. 5 or more exacerbations counted as 5. Further data requested, not yet provided	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	'Restricted' randomisation, balanced blocks
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind. Matching placebo, identified by code number
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	High risk	33% dropout rate
Selective reporting (reporting bias)	Low risk	None detected

Bachh 2007

Methods	Randomised, single-blind, PC, parallel, single-centre. Follow-up 12 months, although treatment given for only 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 ICS permitted at steady dose Exclusions: intolerance of NAC, continuous treatment with OCS, NAC for 3/12 or more, asthma or atopy, other respiratory diseases, NYHA Class II or greater 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 before 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

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Information not available
Allocation concealment (selection bias)	High risk	Single-blind
Blinding of participants and personnel (performance bias) All outcomes	High risk	Single-blind, investigators not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Single-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts recorded
Selective reporting (reporting bias)	Low risk	Main outcomes reported

Boman 1983

Methods	Randomised, DB, PC, parallel, run-in, multi-centre. 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 past 12 months
Interventions	NAC 200 mg BD or placebo
Outcomes	Exacerbations, sick leave due to exacerbations, adverse effects
Notes	Swedish. SD calculated from paper. 6 or more exacerbations counted as 6. Requested more information to calculate effect on sick days, but study authors unable to locate original material

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Done independently at each centre, using a table of random numbers
Allocation concealment (selection bias)	High risk	Investigators aware of order of allocation
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind, but may have been aware of allocation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind, but may have been aware of allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	22% dropout rate (56/259)
Selective reporting (reporting bias)	Low risk	Main outcomes reported

Bontognali 1991

Methods	Randomised, DB, PC. Duration 3 months
Participants	60 participants with chronic bronchitis recruited as inpatients. 63% male. Mean age 57 years. Admission criteria of 20 mL sputum/d with history of 4 or more episodes of acute bronchitis in past 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

Bontognali 1991 (*Continued*)

Outcomes	Exacerbations and duration of acute exacerbations, FEV_1 and FVC, sputum viscosity, adverse effects
Notes	Italian. Surprising that no participants withdrew from study. Huge confidence limits. Possible typographical error in paper, as SD for number of exacerbations per month is the same as for duration of exacerbations. We have used study authors' rates in comparison 01:02 and divided them by months for comparison 01:01

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information not available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	All completed study
Selective reporting (reporting bias)	Unclear risk	Main outcomes not stated viz "efficacy"

Borgia 1981

Methods	Randomised, DB, PC, parallel, multi-centre. PP analysis. Duration 6 months
Participants	21 outpatients with chronic bronchitis defined by MRC and exacerbation in period before the study. Mean age 45.3 years and FEV_1 3.82 litres. Exclusions not stated except FEV_1 < 40%. 2 dropped out
Interventions	NAC 200 mg BD or placebo
Outcomes	Exacerbations, lung function, symptom scores, clinical assessment, adverse effects
Notes	Italian. Published in Italian, therefore reliant on translation. Large differences in baseline rates for lung function

Risk of bias

Borgia 1981 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information not available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	9% dropout rate (2/21), small study
Selective reporting (reporting bias)	Low risk	Main outcomes reported

Castiglioni 1986

Methods	Randomised, DB, PC, parallel, multi-centre (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 younger than 18 or older than 75, FEV_1 < 60%, severe co-morbidity, prior treatment with oral corticosteroids or antibiotics and > 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 participant, adverse effects
Notes	Italian. Requested more information to allow determination of days on antibiotics, not yet provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Done independently at each centre with a table of random numbers to obtain balanced groups
Allocation concealment (selection bias)	High risk	Investigators aware of order of allocation

Castiglioni 1986 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind. Matching placebo but may have been aware of allocation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind but may have been aware of allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	5% dropout rate (33/706)
Selective reporting (reporting bias)	Low risk	Main outcomes reported

Cegla 1988

Methods	Randomised, DB, PC, parallel, multi-centre. 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 of age and patients with asthma, cor pulmonale pulmonary hypertension or polycythaemia < 60%. 23 dropped out. 4 died
Interventions	Ambroxol retard 75 mg daily or placebo
Outcomes	Exacerbations, days sick (off work, in hospital), participant symptoms by diary card, lung function, extra medication use, assessment by investigator and participant, adverse effects
Notes	German. Written in German. Required translation

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Information not available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind

Cegla 1988 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	13% dropout rate (23/180)
Selective reporting (reporting 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)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Information not available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	All completed study
Selective reporting (reporting bias)	Unclear risk	Information not available

De Backer 2013

Methods	Randomised, DB, PC, cross-over. Duration 3 months
Participants	12 outpatients with GOLD stage II or III COPD, age ≥ 40, smoking history at least 10 pack-years but now smoke free, presence of COPD symptoms. 9 men and 3 women with mean age 65, 56 pack-years and FEV_1 65%. All completed study. Exclusions: recent exacerbation, allergy to or prior treatment with NAC, PKU, untreated peptic ulcer, organ insufficiency, ongoing treatment with oral, IV or IM steroids, pregnancy or breastfeeding, treatment with oral cephalosporin
Interventions	NAC 600 mg TDS or placebo
Outcomes	Measured at baseline and at end of each 3/12 treatment period: spirometry, PEFR, raw, NO, specific airway resistance from plethysmography, CT to look at airway geometry, serum glutathione, enzymes, SGRQ, ABG
Notes	Belgian. Funded by an imaging company and a pharmaceutical company Dr Backer works for FluidDA, a functional respiratory imaging company, contracted by Zambon, manufacturer of NAC Responder analysis. Did not report on spirometry or SGRQ results for treatment groups as a whole. These have been requested

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Used computer-generated randomisation list; no further details
Allocation concealment (selection bias)	High risk	Cross-over trial. Trial lasted from August 2009 to June 2012 for only 12 participants. No details on allocation or concealment procedures reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were their own controls. No information about similarity of NAC and placebo
Blinding of outcome assessment (detection bias) All outcomes	High risk	Cross-over trial with no washout period. Possible practice effects. Unsure how blinded investigators were
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed study
Selective reporting (reporting bias)	High risk	Reported responder analysis. Did not report on spirometry or SGRQ results for treatment groups as a whole

Decramer 2005

Methods	Randomised, DB, PC, parallel, multi-centre. 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 2 years before enrolment Exclusions: intolerance of NAC, continuous treatment with oral steroids, NAC for 3/12 or longer, asthma or atopy, other respiratory diseases, NYHA Class II or greater heart failure, GI disease, likely LTOT or lung transplant, alpha 1 antitrypsin deficiency, enrolment in rehab or other study 3 months before 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 value = 0.018)
Interventions	NAC 600 mg daily vs placebo
Outcomes	Yearly reduction in lung function and exacerbation rate Secondary endpoints: quality of life (SGRQ) 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 Data from mixed-effects model used in this study have been provided by Professor De Cramer for total SGRQ scores. Change on NAC was -2.31 and on placebo -3.71. Add these to baseline (using baseline SD) 36.7 (16) and 36.3 (15) to get total SGRQ at end of study to enter into RevMan

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list
Allocation concealment (selection bias)	Low risk	Allocation concealed from study investigators
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind. Identical placebo and active tablets
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind. Investigator unaware of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	70/256 and 99/267 withdrew from mucolytics and placebo, respectively, for 27%

Decramer 2005 (*Continued*)

		dropout rate
Selective reporting (reporting bias)	Low risk	None detected

Ekberg-Jansson 1999

Methods	Randomised, DB, PC, parallel, multi-centre (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 smokers 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
Interventions	N-isobutyrylcysteine (NIC) 300 mg BD or placebo
Outcomes	Time to first exacerbation, exacerbation rate, days sick (judged by participants and investigators), lung function, adverse effects
Notes	European including British. New agent-free thiol donor derivative of NAC

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Information not available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	High risk	21% dropout rate (134/637)
Selective reporting (reporting bias)	Low risk	Reported on main outcomes

Grassi 1976

Methods	Randomised, DB, PC, parallel, multi-centre (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. 3 or more exacerbations counted as 3. 1 to 2 exacerbations counted as 1.5

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Information not available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind. Matching placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	14% dropout rate (11/80)
Selective reporting (reporting bias)	Low risk	Main outcomes reported

Grassi 1994

Methods	Randomised, DB, PC, parallel, multi-centre. PP analysis. Duration 3 months
Participants	135 outpatients with chronic bronchitis with at least 2 exacerbations previous winter randomly assigned to 1 of 3 treatments. Participants aged 40 and 75, mean age 61.8 years, 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. 1 treatment group was intermittent; this is not included in the analysis
Outcomes	Exacerbations, symptoms, sputum characteristics

Grassi 1994 (*Continued*)

Notes	Italian. Published in Italian, therefore relying on translation. SD calculated from paper

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information not available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	3% dropout rate (4/135)
Selective reporting (reporting bias)	Low risk	Main outcomes reported

Grillage 1985

Methods	Randomised, DB, PC, parallel, multi-centre (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 or peptic ulcer and those on mucolytics or steroids. Participants were over 40 years of age, mean PEFR 232 L/min, with 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

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information not available

Grillage 1985 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind. Matching placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	10% dropout rate (11/109)
Selective reporting (reporting bias)	Low risk	Reported on main outcomes

Hansen 1994

Methods	Randomised, DB, PC, parallel, multi-centre (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 past year and $FEV_1 \geq 50\%$ predicted and < 20% reversibility. 100% had smoked. Exclusions were those with atopy or 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
Outcomes	Exacerbations, subjective symptom scores, global well-being, lung function, adverse effects. Did not assess sick days
Notes	Danish

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation in blocks of 4 provided by third party
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind. Matching placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind

Hansen 1994 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	16% dropout rate (24/153)
Selective reporting (reporting bias)	Low risk	Main outcomes reported

Jackson 1984

Methods	Randomised, DB, PC, parallel, multi-centre (16). PP analysis. Duration 3 months	
Participants	155 general practice patients with chronic bronchitis defined by MRC. 88% had smoked. Exclusions were those with other serious respiratory disease or 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	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Information not available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind. Matching placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	High risk	22% dropout rate (34/155)
Selective reporting (reporting bias)	Unclear risk	None detected

Malerba 2004

Methods	Randomised, DB, PC, parallel, multi-centre (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 anticough agents, oral or inhaled corticosteroids not permitted. ICS withdrawn at least 4 weeks before 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 past 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, number of working days lost and number of days of hospitalisation
Notes	Italian. AMETHIST study Post hoc analysis on participants with more severe condition

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Information not available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	14% dropout rate (34/242)
Selective reporting (reporting bias)	Low risk	Main outcomes reported. Some post hoc analysis

McGavin 1985

Methods	Randomised, DB, PC, parallel, multi-centre (26). PP analysis. Duration 5 months
Participants	244 participants entered study, with 200 participants randomly assigned. 181 randomly assigned appropriately (others ineligible or untraceable). Chronic bronchitis defined by MRC, 1 or more exacerbations per year for the past 3 years, FEV_1 < 50% and FEV_1/FVC < 70% predicted. Mean FEV_1 0.86 L. Mean age 63.4 years, 85% male. 99% current smokers or ex-smokers. 148 completed 5 months of 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 study 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

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information not available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind. Matching placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	High risk	39% dropout rate (96/244)
Selective reporting (reporting bias)	Unclear risk	Outcomes not stated clearly, viz "the effect" of ...

Meister 1986

Methods	Randomised, DB, PC, parallel, multi-centre (54). Duration 6 months
Participants	252 outpatients with chronic bronchitis defined by WHO. At least 1 exacerbation in the past winter. 10 patients with asthma and chronic bronchitis were included. Exclusions were those who had received at least 14 days of 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

Meister 1986 (*Continued*)

Interventions	NAC 300 mg BD or placebo
Outcomes	Exacerbations, days sick, concomitant treatment, adverse effects
Notes	German. Provided by Zambon. Not published

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Information not available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	High risk	28% dropout rate (71/252)
Selective reporting (reporting bias)	High risk	Not published

Meister 1999

Methods	Randomised, DB, PC, parallel, multi-centre (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 past winter. Exclusions were those who 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

Meister 1999 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Information not available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind. Matched placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	17% dropout rate (42/246)
Selective reporting (reporting bias)	Low risk	Reported on main outcomes both PP and ITT

Moretti 2004

Methods	Randomised, DB, PC, parallel, multi-centre (9). PP analysis reported. Duration 8 months
Participants	155 outpatients with COPD defined by ERS. Age 25 to 85 years; 1 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 co-morbidity; asthma; known poor compliance Mean age 67 years, 80% male, 33% smokers, FEV_1 after salbutamol 1.68 L (SD 0.31) in erdosteine group and 1.59 L (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 (SGRQ), pharmacoeconomic analysis
Notes	Italian. EQUALIFE study Mucolytic group had (insignificantly) more males and better lung function at baseline
Risk of bias	

Moretti 2004 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information not available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	High risk	20% dropout rate (31/155)
Selective reporting (reporting bias)	Low risk	Reported all primary outcomes

Nowak 1999

Methods	Randomised, DB, PC, parallel, multi-centre (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. Participant symptoms, adverse effects
Notes	European. COPD, not chronic bronchitis. BREATHE study. Published in abstract form only. Zambon provided more information. Study never published in full

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information not available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind

Nowak 1999 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	6% dropout rate (18/313)
Selective reporting (reporting bias)	High risk	Information not available

Olivieri 1987

Methods	Randomised, DB, PC, parallel, multi-centre (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 < 40% predicted, peptic ulcer or other serious co-morbidity, 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 participant global assessments, laboratory data, adverse effects
Notes	Italian. We suspect that what is reported as SD in the paper is in fact SE (using t statistic and P values). We have written to study authors for clarification. No reply received

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-randomised
Allocation concealment (selection bias)	Unclear risk	Each centre provided with a list
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	11% dropout rate (26/240)

Olivieri 1987 (*Continued*)

Selective reporting (reporting bias)	Low risk	PP and ITT analysis of all main outcomes

Parr 1987

Methods	Randomised, DB, PC, parallel, multi-centre. PP analysis. Duration 6 months
Participants	526 general practice patients with chronic bronchitis defined by MRC, with at least 1 exacerbation in past 12 months. Patients were excluded for other significant respiratory disease, active peptic ulceration, severe heart failure or continuous therapy with antibiotics or mucolytics. 204 dropouts. Mean age 63 years, 66% male, 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 paper. Need more data to calculate days sick

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomly assigned in blocks of 4
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind. Interventions identical
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	High risk	39% dropout rate (204/526)
Selective reporting (reporting bias)	Unclear risk	No specific outcomes stated

Pela 1999

Methods	Randomised, open, PC, parallel, multi-centre (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, participant preference, lung function
Notes	Italian study. Open study. COPD, not chronic bronchitis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details
Allocation concealment (selection bias)	High risk	Investigators aware of order of allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	9% dropout rate (6/69)
Selective reporting (reporting bias)	Low risk	Reported on main outcomes

Petty 1990

Methods	Randomised, DB, PC, parallel, multi-centre. Duration 2 months. ITT analysis
Participants	367 outpatients with stable chronic bronchitis defined by American Thoracic Society were randomly assigned. Required pre-bronchodilator FEV_1 < 75% predicted. 79 drop-outs (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 co-morbidity that would confound response or compliance, with asthma and 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

Petty 1990 (*Continued*)

Outcomes	Investigator assessment of symptoms, participant evaluation of symptoms, global assessment at weeks 0, 4 and 8, frequency of bronchodilator use, number and duration of acute exacerbations, frequency of concomitant medications, adverse experiences. Drop-outs assessed at weeks 4 and 8
Notes	American. Requested more information from study author, but unable to provide. Pharmaceutical company (Wallace) approached. No reply. No significant differences (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 have assumed equal variances to arrive at an estimate for SD of 18.8

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind. Matched placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	High risk	22% dropout rate (79/367)
Selective reporting (reporting bias)	Low risk	None detected

Rasmussen 1988

Methods	Randomised, DB, PC, parallel, multi-centre (9). PP analysis. Duration 6 months
Participants	116 outpatients with chronic bronchitis defined by MRC. At least 1 exacerbation previous winter. 100% had smoked. Mean age 58.9 years, 57% male, average PEFR of 305 litres/min. 25 dropped out
Interventions	NAC 300 mg BD or placebo
Outcomes	Exacerbations, days sick evaluated by days on sick list and by participant diaries, adverse effects
Notes	Swedish

Rasmussen 1988 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation in blocks of 4
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	High risk	22% dropout rate (25/116)
Selective reporting (reporting bias)	Low risk	Main outcomes reported

Roy 2014

Methods	Randomised, single-blind, PC, parallel, single-centre. PP analysis. Duration 6 months Followed up every month
Participants	80 outpatients with age > 40, stable mild to moderate COPD, smoking history at least 10 pack-years. Excluded were those with asthma, lung cancer, cardiomyopathy, LVRS or transplant or on LTOT or corticosteroids. Mean age 61, 89% male. Total of 20 dropouts, evenly matched between groups
Interventions	NAC 600 mg BD or placebo. Both groups received a bronchodilator Deriphylline Retard 150 mg in addition
Outcomes	Symptoms (cough, dyspnoea, sputum), spirometry, Hb, adverse events
Notes	Indian Funding source not reported

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	No details on this, except it was a "simple method"

Roy 2014 (*Continued*)

Allocation concealment (selection bias)	High risk	Single-blind study. Few details given on allocation or concealment of sequence
Blinding of participants and personnel (performance bias) All outcomes	High risk	No details on match between placebo and NAC, or on who performed measurements. SIngle-blind
Blinding of outcome assessment (detection bias) All outcomes	High risk	SIngle-blind study
Incomplete outcome data (attrition bias) All outcomes	High risk	25% dropout rate (20/80)
Selective reporting (reporting bias)	Unclear risk	Spirometric data reported in units that read "total count"

Schermer 2009

Methods	Randomised, DB, PC, parallel, multi-centre (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 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 history of asthma, allergic rhinitis or eczema 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 smoking. 22% had 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 Participants well matched at baseline. High dropout rate. Generally low exacerbation rates, except small number of participants who experienced very frequent exacerbations
Interventions	3 arms, double-dummy (tablet and inhaler). NAC 600 mg effervescent tablet daily vs fluticasone 500 mcg BD vs placebo. This review included only NAC vs placebo arms. 2 weeks of pretreatment with prednisone 30 mg daily
Outcomes	Primary outcomes: rates of exacerbation and disease-specific quality of life, as measured by CRQ Other outcomes: lung function and hospitalisation
Notes	

Risk of bias

Schermer 2009 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	List generated by independent statistician
Allocation concealment (selection bias)	Low risk	Neither participants nor investigators aware of allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-dummy
Incomplete outcome data (attrition bias) All outcomes	High risk	44% dropout rate (44/96 and 40/97 dropped out on mucolytics and placebo, respectively)
Selective reporting (reporting bias)	Low risk	None detected

Tse 2013

Methods	Randomised, DB, PC, parallel, 1 hospital centre. Duration 1 year 4 week run-in period, randomisation, then follow-up at 16, 32 and 48 weeks Analysis ITT
Participants	133 outpatients aged 50 to 80 with stable COPD (FEV_1/FVC < 0.7). Exclusion criteria were co-existent pulmonary disease, LTOT, BiPAP, severe dyspnoea and poor reliability or compliance. Mean age 71, 93% male, 23% current smokers 18% GOLD 1, 40% GOLD 2, 34% GOLD 3, 8% GOLD 4. Median of 2 exacerbations in past year. Groups were well matched at baseline. 12 dropouts - 6 in each group
Interventions	NAC 600 mg BD or placebo
Outcomes	Primary: small airways parameters $FEF_{25\%-75\%}$, FOT, IC, spirometry Secondary: exacerbation rate, mMRC dyspnoea scale, SGRQ, 6MWD
Notes	Chinese (Hong Kong). HIACE study. Funded by pharmaceutical company Funding from local hospital research fund. Zambon provided NAC and placebo. 1 study author (Dr Ratieri) is employed by Zambon

Risk of bias

Bias	Authors' judgement	Support for judgement

Tse 2013 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	No detail on this
Allocation concealment (selection bias)	Unclear risk	Not well described: "randomisation and allocation details known only to a third party"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	NAC and placebo "identical in appearance"; "patients and investigators blinded to treatment allocation during the study". Compliance assessed
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Patients and investigators blinded to treatment allocation during the study"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	19% dropout rate (25/133). Flow chart of dropout numbers and reasons
Selective reporting (reporting bias)	Low risk	All major outcomes reported in detail

Worth 2009

Methods	Randomised, DB, PC, parallel, multi-centre (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; 64% were male. Mean FEV_1 1.61 L (54.7% predicted). Excluded were patients with severe medical conditions such as bronchial carcinoma, MI, alcoholism or heart failure Unclear how many participants finished the study Groups well matched at baseline. Compliance said to be 'good' in all participants	
Interventions	Cineole 2 × 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	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Worth 2009 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Apart from an indication of stratification by site, no details given on randomisation methods
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants instructed to take medication half hour before meals to avoid the smell of cineole. Active and placebo capsules looked identical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No details on dropouts
Selective reporting (reporting bias)	Low risk	None apparent

Zheng 2008

Methods	Randomised, DB, PC, parallel, multi-centre (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. 91 dropouts (48 in mucolytic group and 43 in placebo group). Mean age 65 years, 78% male, mean FEV_1 1.09 L (44.5% predicted). 75% had ever smoked. 49% were GOLD 2, 39% GOLD 3 and 12% GOLD 4. Mean SGRQ was 42. Excluded were patients with asthma, non-COPD respiratory disorders, LVRS or transplant or other conditions that would interfere with the study, and those on LTOT or pulmonary rehabilitation, on OCS, with pregnancy or lactating. Patients involved in another investigational drug trial in past 12 weeks were also excluded 18% of intervention group and 15% of placebo group were on ICS
Interventions	Carbocysteine 1500 mg daily (2 × 250 mg TDS) orally or placebo
Outcomes	Primary endpoint: exacerbation rate (defined by Anthonisen). Secondary endpoints: co-variance-adjusted exacerbation rate, quality of life (SGRQ), lung function and arterial oxygen saturation
Notes	Chinese, main PEACE study. Financial support from Kyron Pharmaceutical, Japan *Lancet* report for main PEACE study describes 709 participants from 22 centres in China. Another 2 references to PEACE study from Japan (Tatsumi 2007a; Tatsumi 2007b). Both refer to same sample of 142 patients - 70 in control group and 72 in study group. Have written to Dr Zhong to ask if a substudy of main PEACE study - was a different study

Zheng 2008 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Computer-generated randomisation list"
Allocation concealment (selection bias)	Low risk	"Neither the investigator nor the patient knew the group allocation"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The placebo was identical to the drug in appearance labelling and packaging"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Statistical analysis done without awareness of treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	13% dropout rate (48/353 and 43/354 withdrew from mucolytics and placebo, respectively)
Selective reporting (reporting bias)	Low risk	None apparent

Zheng 2014

Methods	Randomised, DB, PC, parallel, multi-centre (34 centres). Duration 1 year 2 week run-in period, then randomisation and visits at 1, 2, 6, 9, 12 months. Analysis conducted on "patients who received at one dose of study drug, and had at least one visit assessment after randomisation." This ended up being 482 in each group (total 964). Completers totaled 763. Did not outline methods for handling missing data
Participants	From 1297 screened, investigators enrolled 1006 outpatients aged 40 to 80 with moderate to severe COPD (FEV_1< 30% to 70% predicted and ratio < 0.7). These were stratified by previous regular use of ICS at baseline (500 to 2000 mcg/d of beclomethasone or equivalent). Exclusion criteria: bronchial asthma, LTOT $\geq$ 12 hours per day or pulmonary rehabilitation, major co-morbidity, poor reliability or compliance. Ratio of ICS users to ICS naïve participants was set at about 4:6 Groups were well matched at baseline. Mean age 66 years, 82% male, 76% ever smokers, mean FEV_1 49% predicted. 46% GOLD 2, 53% GOLD 3 and 1% GOLD 4. 243 dropouts - 124 in treatment group and 119 in placebo group - with main reasons being loss to follow-up and adverse events. Provided analysis of dropouts (N = 243) vs completers (N = 763) - similar among the 2 groups
Interventions	NAC 600 mg TDS or placebo

Outcomes	Primary: exacerbation rate in 1 year, exacerbation duration Secondary: time to first exacerbation, time to recurrent exacerbation, number of participants requiring systemic corticosteroids or antibiotics or use of SABA rescue medication, SGRQ (Chinese version), spirometry, adverse events (including hospitalisation or death)
Notes	Chinese, PANTHEON study. Funded by a pharmaceutical company (Hainan Zambon Pharmaceutical). Study authors had full access to all data and were involved in data interpretation and preparation of manuscript in collaboration with sponsor. Corresponding authors had final responsibility for decision to submit for publication Dr Zheng provided Appendix, as well as further data on exacerbation rates, SQRG scores and spirometry

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Stratified randomisation conducted using a pre-determined computer-generated randomisation list provided by a statistician from a third party not involved in the study. This third party was exclusively responsible for randomisation, data management, data analysis and data quality control
Allocation concealment (selection bias)	Low risk	Supplies of tablets for every participant were identified by a 4-digit number. A sealed envelope containing the randomisation code for each participant was kept by the investigator and was not to be opened during the study, unless a serious life-threatening adverse event occurred
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both NAC and placebo tablets were provided by Hainan Zambon Pharmaceutical Co., Ltd. The placebo was identical in composition, shape, color and size but did not contain any active ingredients. NAC and placebo tablets were packaged and labelled in such a way that they could not be distinguished from each other
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All investigators were trained before the trial to ensure reliable study quality, with special emphasis on understanding the protocol, performing spirometry tests, blinding to allocation, managing the drug supply and maintaining compliance with Good Clinical Practice (GCP). Details of study

		design were published ahead of the study results
Incomplete outcome data (attrition bias) All outcomes	High risk	24% dropout rate (243/1006)
Selective reporting (reporting bias)	Low risk	CONSORT statement was followed to ensure proper reporting of this study

ATS: American Thoracic Society; BD: twice daily; BiPAP: bi-level non-invasive ventilation; 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; $FEF_{25\%-75\%}$: forced expiratory flow; FEV_1: forced expiratory volume in one second; FOT: forced oscillation technique; FVC: forced vital capacity; GI: gastrointestinal; GOLD: Global Initiative for Obstructive Lung Disease; IC: inspiratory capacity; 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; SABA: short-acting beta-agonist; 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; 6MWD: six-minute walk distance.

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

Study	Reason for exclusion
Baglioni 2001	Preliminary, small, open RCT of NAC vs placebo in patients on LTOT, published in abstract form only, with 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 patients with asthma and patients with COPD
Kasielski 2001	Did not evaluate clinical outcomes
Lukas 2005	Translated from German. Patients with chronic bronchitis given NAC, placebo, Vit C or NAC + Vit C for 3 months. Did not evaluate primary outcome. Outcomes were lung function, symptoms, neutrophils and other blood outcomes such as oxidising ability. No numerical data presented on lung function or symptoms, although study authors reported no differences for either of these
Maesen 1980	Did not evaluate primary outcome

(*Continued*)

Michnar 1996	Did not evaluate primary outcome
Moretti 2011	Acute setting, 10 days of treatment with erdosteine
Rubin 1996	Did not evaluate primary outcome
Tatsumi 2007a	Even though randomised, not placebo-controlled
Tatsumi 2007b	Even though randomised, not placebo-controlled
Velazquez 2001	Only 4 weeks long
Wilhelmi 2010	Has been translated from German. Patients with COPD given cineole or placebo for 6 months. Evaluated primary outcome of exacerbations; although P values given for a significant reduction in exacerbations in cineole group compared with placebo, no data were supplied for event rates. Appears to be a short report summarising original trial

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 Participants with no exacerbations in study period	26	6233	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.75 [1.57, 1.94]
1.1 Double-blind	24	5970	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.71 [1.53, 1.90]
1.2 Single-blind/open	2	263	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.91 [1.76, 4.83]
2 Participants with no exacerbation by decade, db trials only	24	5970	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.71 [1.53, 1.90]
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	7	2561	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.21 [1.03, 1.43]
3 Participants 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]
3.1 Double-blind	20	3844	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.18 [1.91, 2.49]
3.2 Single-blind/open	1	163	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.85 [1.49, 5.46]
4 Number of exacerbations per participant per month	28	7164	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.04, -0.03]
4.1 Double-blind	27	7095	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.04, -0.03]
4.2 Single-blind/open	1	69	Mean Difference (IV, Fixed, 95% CI)	-0.13 [-0.22, -0.04]
5 Number of exacerbations per participant per month, by type or dose of mucolytic	28		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 N-acetylcysteine	15	4046	Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.05, -0.03]
5.2 N-acetylcysteine 400 mg daily	3	717	Mean Difference (IV, Fixed, 95% CI)	-0.18 [-0.21, -0.14]
5.3 N-acetylcysteine 600 mg daily	10	2236	Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.03, -0.01]
5.4 N-acetylcysteine 1200 mg daily	2	249	Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.10, -0.00]
5.5 N-acetylcysteine 1800 mg daily	1	964	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.05, -0.01]
5.6 Carbocysteine	4	1340	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.04, -0.02]
5.7 Other mucolytic	8	1752	Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.06, -0.03]
6 Number of exacerbations per participant per month, by FEV_1	19	5660	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.04, -0.02]
6.1 Studies with mean FEV_1 $\leq$ 50% predicted	3	1326	Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.06, -0.02]
6.2 Studies with mean FEV_1 > 50% predicted	16	4334	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.04, -0.02]
7 Number of exacerbations per participant per month, no ICS	3	581	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.01, 0.04]
7.1 Not taking inhaled corticosteroids	3	581	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.01, 0.04]

8 Number of exacerbations per participant per month, by study duration	28	7258	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.04, -0.03]
8.1 Duration ≤ 3 months	5	918	Mean Difference (IV, Fixed, 95% CI)	-0.13 [-0.17, -0.09]
8.2 Duration > 3 months and < 12 months	18	3720	Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.07, -0.05]
8.3 Duration ≥ 12 months	5	2620	Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.02, -0.01]
9 Number of exacerbations per participant per month, by country	28	7258	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.04, -0.03]
9.1 Italian	12	2556	Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.07, -0.05]
9.2 Non-Italian	16	4702	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.03, -0.02]
10 Number of exacerbations per participant per month, in participants included for history of exacerbation	19	5224	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.04, -0.02]
11 Days of disability per participant per month	13	3269	Mean Difference (IV, Fixed, 95% CI)	-0.43 [-0.56, -0.30]
12 Days on antibiotics per participant per month	3	714	Mean Difference (IV, Fixed, 95% CI)	-0.53 [-0.76, -0.31]
13 Health-related quality of life (total score St George Respiratory Questionnaire)	5	2231	Mean Difference (IV, Fixed, 95% CI)	-2.60 [-4.29, -0.90]
14 Hospitalisation during study period	4	1788	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.68 [0.52, 0.89]
15 FEV_1 or % predicted FEV_1 or PEFR at end of study	18	3974	Std. Mean Difference (IV, Fixed, 95% CI)	0.09 [0.02, 0.16]
15.1 Double-blind	15	3651	Std. Mean Difference (IV, Fixed, 95% CI)	0.08 [0.00, 0.15]
15.2 Single-blind	3	323	Std. Mean Difference (IV, Fixed, 95% CI)	0.19 [-0.03, 0.41]
16 FVC at end of study	10	2616	Mean Difference (IV, Fixed, 95% CI)	0.05 [0.03, 0.08]
17 Adverse effects	21	6346	Odds Ratio (M-H, Fixed, 95% CI)	0.88 [0.78, 1.00]
18 Death during study period	8	2931	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.03 [0.52, 2.03]

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 participant per month	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Participants with no exacerbations in the study period	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
3 Days of disability per participant 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 Participants with no exacerbations in study period.

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

Comparison: 1 Mucolytic versus placebo

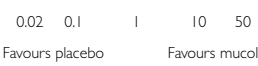
Outcome: 1 Participants with no exacerbations in study period

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		1.2 %	2.16 [0.84, 5.59]
Babolini 1980	134/254	58/241		8.4 %	3.34 [2.33, 4.79]
Borgia 1981	7/10	4/9		0.3 %	2.70 [0.46, 15.93]
Boman 1983	46/98	29/105		3.4 %	2.28 [1.29, 4.03]
Jackson 1984	41/61	36/60		2.0 %	1.36 [0.65, 2.85]
Grillage 1985	35/54	29/55		1.9 %	1.64 [0.77, 3.50]
McGavin 1985	11/72	8/76		1.2 %	1.52 [0.58, 3.98]
Cremonini 1986	8/21	0/20		0.5 %	10.66 [2.32, 49.05]
Meister 1986	37/90	34/91		3.1 %	1.17 [0.64, 2.12]
Castiglioni 1986	240/311	179/302		9.5 %	2.28 [1.63, 3.21]
Olivieri 1987	56/110	21/104		3.5 %	3.77 [2.16, 6.58]
Rasmussen 1988	28/44	24/47		1.6 %	1.66 [0.73, 3.80]
Hansen 1994	36/59	34/70		2.3 %	1.64 [0.82, 3.29]
Grassi 1994	25/42	14/41		1.5 %	2.74 [1.16, 6.45]
Allegra 1996	111/171	89/181		6.2 %	1.90 [1.24, 2.89]
Meister 1999	79/122	56/124		4.4 %	2.20 [1.33, 3.63]
Nowak 1999	114/147	101/148		4.2 %	1.60 [0.96, 2.67]
Moretti 2004	26/63	13/61		1.9 %	2.50 [1.18, 5.33]
Malerba 2004	64/115	63/119		4.2 %	1.11 [0.67, 1.86]
Zheng 2008	159/353	151/354		12.5 %	1.10 [0.82, 1.48]
Schermer 2009	22/96	27/96		2.6 %	0.76 [0.40, 1.45]
Worth 2009	79/110	60/110		3.7 %	2.09 [1.21, 3.62]
Tse 2013	28/58	21/62		2.1 %	1.81 [0.87, 3.73]
Zheng 2014	130/482	122/482		13.4 %	1.09 [0.82, 1.45]

(*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
Subtotal (95% CI)	**2978**	**2992**	♦	**95.7 %**	**1.71 [1.53, 1.90]**
Total events: 1534 (Mucolytic), 1184 (Placebo)					
Heterogeneity: Chi^2 = 63.23, df = 23 (P = 0.00001); I^2 =64%					
Test for overall effect: Z = 9.77 (P < 0.00001)					
2 Single-blind/open					
Pela 1999	37/83	17/80	—	2.6 %	2.85 [1.49, 5.46]
Bachh 2007	25/50	12/50	—	1.7 %	3.02 [1.35, 6.77]
Subtotal (95% CI)	**133**	**130**	◆	**4.3 %**	**2.91 [1.76, 4.83]**
Total events: 62 (Mucolytic), 29 (Placebo)					
Heterogeneity: Chi^2 = 0.01, df = 1 (P = 0.91); I^2 =0.0%					
Test for overall effect: Z = 4.14 (P = 0.000035)					
Total (95% CI)	**3111**	**3122**	♦	**100.0 %**	**1.75 [1.57, 1.94]**
Total events: 1596 (Mucolytic), 1213 (Placebo)					
Heterogeneity: Chi^2 = 67.33, df = 25 (P<0.00001); I^2 =63%					
Test for overall effect: Z = 10.42 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 4.09, df = 1 (P = 0.04), I^2 =76%					

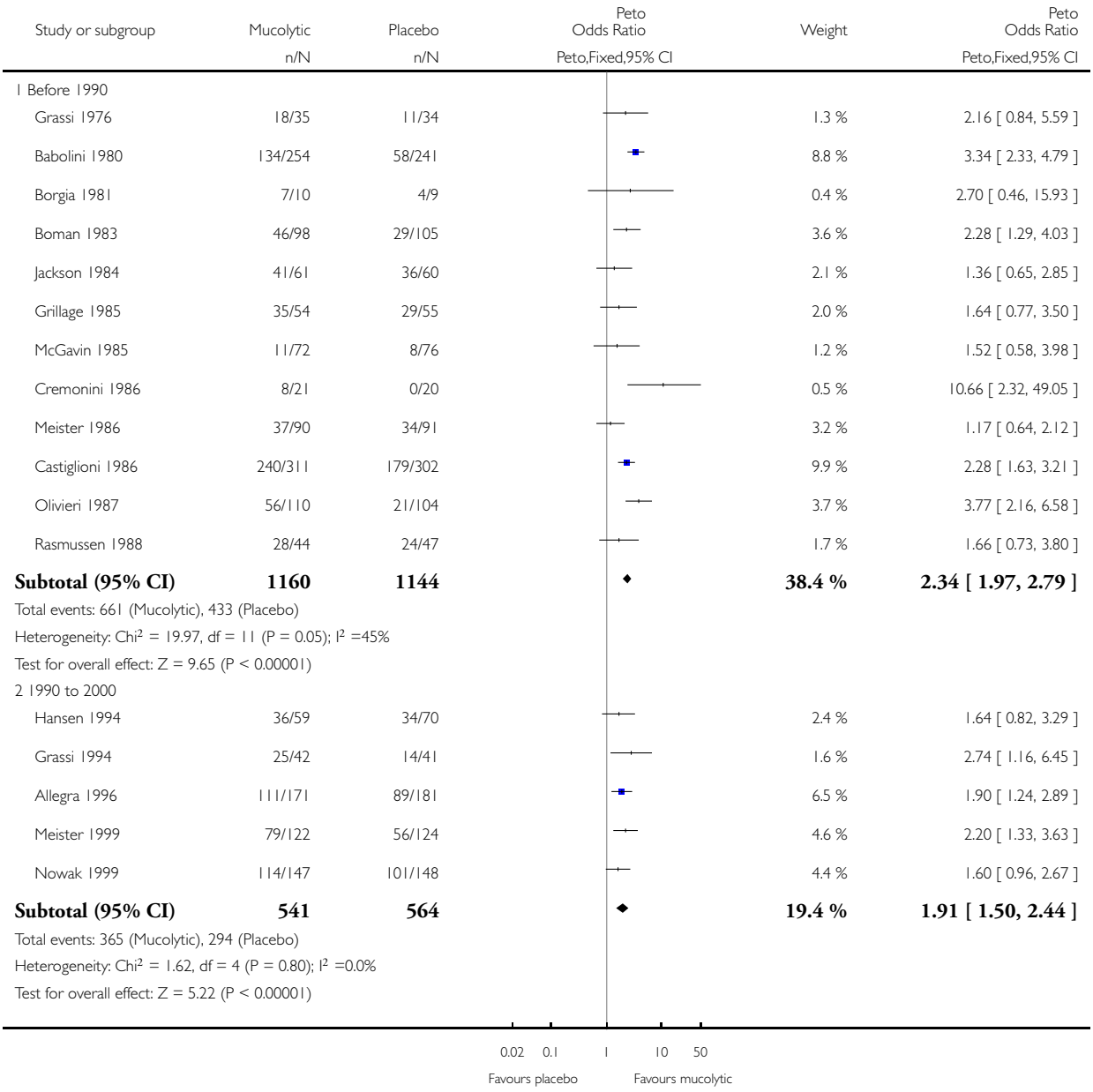


Analysis 1.2. Comparison 1 Mucolytic versus placebo, Outcome 2 Participants with no exacerbation by decade, db trials only.

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

Comparison: 1 Mucolytic versus placebo

Outcome: 2 Participants with no exacerbation by decade, db trials only



(*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
3 2000 onwards					
Malerba 2004	64/115	63/119		4.4 %	1.11 [0.67, 1.86]
Moretti 2004	26/63	13/61		2.0 %	2.50 [1.18, 5.33]
Zheng 2008	159/353	151/354		13.1 %	1.10 [0.82, 1.48]
Worth 2009	79/110	60/110		3.8 %	2.09 [1.21, 3.62]
Schermer 2009	22/96	27/96		2.7 %	0.76 [0.40, 1.45]
Tse 2013	28/58	21/62		2.2 %	1.81 [0.87, 3.73]
Zheng 2014	130/482	122/482		13.9 %	1.09 [0.82, 1.45]
Subtotal (95% CI)	**1277**	**1284**		**42.2 %**	**1.21 [1.03, 1.43]**
Total events: 508 (Mucolytic), 457 (Placebo)					
Heterogeneity: Chi^2 = 11.56, df = 6 (P = 0.07); I^2 =48%					
Test for overall effect: Z = 2.30 (P = 0.021)					
Total (95% CI)	**2978**	**2992**		**100.0 %**	**1.71 [1.53, 1.90]**
Total events: 1534 (Mucolytic), 1184 (Placebo)					
Heterogeneity: Chi^2 = 63.23, df = 23 (P = 0.00001); I^2 =64%					
Test for overall effect: Z = 9.77 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 30.07, df = 2 (P = 0.00), I^2 =93%					

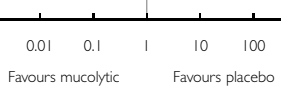
Analysis 1.3. Comparison 1 Mucolytic versus placebo, Outcome 3 Participants with no exacerbations in the study period - winter treatment only.

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

Comparison: 1 Mucolytic versus placebo

Outcome: 3 Participants 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					



(*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
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 1.4. Comparison 1 Mucolytic versus placebo, Outcome 4 Number of exacerbations per participant per month.

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

Comparison: 1 Mucolytic versus placebo

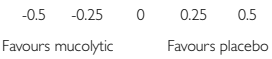
Outcome: 4 Number of exacerbations per participant per month

Study or subgroup	Mucolytic N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 Double-blind							
Grassi 1976	35	0.14 (0.15)	34	0.27 (0.21)		0.6 %	-0.13 [-0.22, -0.04]
Babolini 1980	254	0.13 (0.18)	241	0.33 (0.27)		2.7 %	-0.20 [-0.24, -0.16]
Borgia 1981	10	0.05 (0.08)	9	0.15 (0.17)		0.3 %	-0.10 [-0.22, 0.02]
Boman 1983	98	0.2 (0.27)	105	0.32 (0.3)		0.7 %	-0.12 [-0.20, -0.04]
Jackson 1984	61	0.11 (0)	60	0.13 (0)			Not estimable
Grillage 1985	54	0.1 (0)	55	0.12 (0)			Not estimable
McGavin 1985	72	0.42 (0.34)	76	0.52 (0.35)		0.4 %	-0.10 [-0.21, 0.01]
Meister 1986	90	0.15 (0.15)	91	0.2 (0.19)		1.8 %	-0.05 [-0.10, 0.00]
Cremonini 1986	21	0.25 (0.23)	20	0.71 (0.29)		0.2 %	-0.46 [-0.62, -0.30]
Castiglioni 1986	311	0.1 (0.21)	302	0.2 (0.29)		2.7 %	-0.10 [-0.14, -0.06]
Olivieri 1987	110	0.18 (0.31)	104	0.33 (0.41)		0.5 %	-0.15 [-0.25, -0.05]
Parr 1987	243	0.18 (0.21)	210	0.21 (0.21)		2.9 %	-0.03 [-0.07, 0.01]
Rasmussen 1988	44	0.13 (0.21)	47	0.14 (0.19)		0.6 %	-0.01 [-0.09, 0.07]
Bontognali 1991	30	0.7 (3.76)	30	1.27 (4.58)		0.0 %	-0.57 [-2.69, 1.55]
Grassi 1994	42	0.16 (0.29)	41	0.45 (0.43)		0.2 %	-0.29 [-0.45, -0.13]
Hansen 1994	59	0.11 (0.15)	70	0.16 (0.19)		1.3 %	-0.05 [-0.11, 0.01]
Allegra 1996	223	0.07 (0.11)	218	0.11 (0.14)		7.9 %	-0.04 [-0.06, -0.02]
Nowak 1999	147	0.03 (0.06)	148	0.06 (0.12)		9.4 %	-0.03 [-0.05, -0.01]
Meister 1999	122	0.06 (0.15)	124	0.1 (0.15)		3.1 %	-0.04 [-0.08, 0.00]
Malerba 2004	115	0.06 (0.08)	119	0.07 (0.08)		10.4 %	-0.01 [-0.03, 0.01]
Moretti 2004	63	0.12 (0.14)	61	0.17 (0.17)		1.5 %	-0.05 [-0.10, 0.00]
Decramer 2005	256	0.1 (0.11)	267	0.11 (0.16)		8.0 %	-0.01 [-0.03, 0.01]
Zheng 2008	353	0.08416 (0.094)	354	0.11 (0.094)		22.8 %	-0.03 [-0.04, -0.01]

(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Mucolytic N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Worth 2009	110	0.067 (0.136)	110	0.15 (0.24)		1.6 %	-0.08 [-0.13, -0.03]
Schermer 2009	96	0.08 (0.1)	96	0.06 (0.05)		8.8 %	0.02 [0.00, 0.04]
Zheng 2014	482	0.1 (0.15)	482	0.13 (0.17)		10.7 %	-0.03 [-0.05, -0.01]
Tse 2013	58	0.08 (0.24)	62	0.14 (0.24)		0.6 %	-0.06 [-0.15, 0.03]
Subtotal (95% CI)	**3559**		**3536**			**99.4 %**	**-0.03 [-0.04, -0.03]**
Heterogeneity: Chi^2 = 167.14, df = 24 (P<0.00001); I^2 =86%							
Test for overall effect: Z = 10.14 (P < 0.00001)							
2 Single-blind/open							
Pela 1999	35	0.14 (0.15)	34	0.27 (0.21)		0.6 %	-0.13 [-0.22, -0.04]
Subtotal (95% CI)	**35**		**34**			**0.6 %**	**-0.13 [-0.22, -0.04]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.95 (P = 0.0032)							
Total (95% CI)	**3594**		**3570**			**100.0 %**	**-0.03 [-0.04, -0.03]**
Heterogeneity: Chi^2 = 171.83, df = 25 (P<0.00001); I^2 =85%							
Test for overall effect: Z = 10.34 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 4.69, df = 1 (P = 0.03), I^2 =79%							



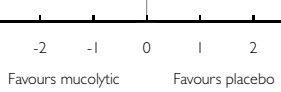
Analysis 1.5. Comparison 1 Mucolytic versus placebo, Outcome 5 Number of exacerbations per participant per month, by type or dose of mucolytic.

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

Comparison: 1 Mucolytic versus placebo

Outcome: 5 Number of exacerbations per participant 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	Weight	Mean Difference IV,Fixed,95% CI
1 N-acetylcysteine							
Babolini 1980	254	0.13 (0.18)	241	0.33 (0.27)		6.0 %	-0.20 [-0.24, -0.16]
Boman 1983	98	0.2 (0.27)	105	0.32 (0.3)		1.6 %	-0.12 [-0.20, -0.04]
Borgia 1981	10	0.05 (0.08)	9	0.15 (0.17)		0.7 %	-0.10 [-0.22, 0.02]
Decramer 2005	256	0.1 (0.11)	267	0.11 (0.16)		18.2 %	-0.01 [-0.03, 0.01]
Grassi 1976	35	0.14 (0.15)	34	0.27 (0.21)		1.3 %	-0.13 [-0.22, -0.04]
Hansen 1994	59	0.11 (0.15)	70	0.16 (0.19)		2.9 %	-0.05 [-0.11, 0.01]
Jackson 1984	61	0.11 (0)	60	0.13 (0)			Not estimable
McGavin 1985	72	0.42 (0.34)	76	0.52 (0.35)		0.8 %	-0.10 [-0.21, 0.01]
Meister 1986	90	0.15 (0.15)	91	0.2 (0.19)		4.0 %	-0.05 [-0.10, 0.00]
Nowak 1999	147	0.03 (0.06)	148	0.06 (0.12)		21.4 %	-0.03 [-0.05, -0.01]
Parr 1987	243	0.18 (0.21)	210	0.21 (0.21)		6.6 %	-0.03 [-0.07, 0.01]
Pela 1999	83	0.17 (0.18)	80	0.29 (0.32)		1.6 %	-0.12 [-0.20, -0.04]
Rasmussen 1988	44	0.13 (0.21)	47	0.14 (0.19)		1.5 %	-0.01 [-0.09, 0.07]
Schermer 2009	96	0.08 (0.14)	96	0.06 (0.09)		9.0 %	0.02 [-0.01, 0.05]
Zheng 2014	482	0.1 (0.15)	482	0.13 (0.17)		24.4 %	-0.03 [-0.05, -0.01]
Subtotal (95% CI)	**2030**		**2016**			**100.0 %**	**-0.04 [-0.05, -0.03]**
Heterogeneity: Chi^2 = 95.05, df = 13 (P<0.00001); I^2 =86%							
Test for overall effect: Z = 7.54 (P < 0.00001)							
2 N-acetylcysteine 400 mg daily							
Babolini 1980	254	0.13 (0.18)	241	0.33 (0.27)		72.4 %	-0.20 [-0.24, -0.16]
Boman 1983	98	0.2 (0.27)	105	0.32 (0.3)		19.5 %	-0.12 [-0.20, -0.04]
Borgia 1981	10	0.05 (0.08)	9	0.15 (0.17)		8.1 %	-0.10 [-0.22, 0.02]
Subtotal (95% CI)	**362**		**355**			**100.0 %**	**-0.18 [-0.21, -0.14]**
Heterogeneity: Chi^2 = 4.80, df = 2 (P = 0.09); I^2 =58%							
Test for overall effect: Z = 9.99 (P < 0.00001)							
3 N-acetylcysteine 600 mg daily							



(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Mucolytic N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Decramer 2005	256	0.1 (0.11)	267	0.11 (0.16)		24.1 %	-0.01 [-0.03, 0.01]
Grassi 1976	35	0.14 (0.15)	34	0.27 (0.21)		1.8 %	-0.13 [-0.22, -0.04]
Jackson 1984	61	0.11 (0)	60	0.13 (0)			Not estimable
McGavin 1985	72	0.42 (0.34)	76	0.52 (0.35)		1.1 %	-0.10 [-0.21, 0.01]
Meister 1986	90	0.15 (0.15)	91	0.2 (0.19)		5.3 %	-0.05 [-0.10, 0.00]
Nowak 1999	147	0.03 (0.06)	148	0.06 (0.12)		28.3 %	-0.03 [-0.05, -0.01]
Parr 1987	243	0.18 (0.21)	210	0.21 (0.21)		8.8 %	-0.03 [-0.07, 0.01]
Pela 1999	83	0.17 (0.18)	80	0.29 (0.32)		2.1 %	-0.12 [-0.20, -0.04]
Rasmussen 1988	44	0.13 (0.21)	47	0.14 (0.19)		1.9 %	-0.01 [-0.09, 0.07]
Schermer 2009	96	0.08 (0.1)	96	0.06 (0.05)		26.5 %	0.02 [0.00, 0.04]
Subtotal (95% CI)	**1127**		**1109**			**100.0 %**	**-0.02 [-0.03, -0.01]**
Heterogeneity: Chi^2 = 29.46, df = 8 (P = 0.00026); I^2 =73%							
Test for overall effect: Z = 2.89 (P = 0.0038)							
4 N-acetylcysteine 1200 mg daily							
Hansen 1994	59	0.11 (0.15)	70	0.16 (0.19)		68.2 %	-0.05 [-0.11, 0.01]
Tse 2013	58	0.08 (0.24)	62	0.14 (0.24)		31.8 %	-0.06 [-0.15, 0.03]
Subtotal (95% CI)	**117**		**132**			**100.0 %**	**-0.05 [-0.10, 0.00]**
Heterogeneity: Chi^2 = 0.04, df = 1 (P = 0.85); I^2 =0.0%							
Test for overall effect: Z = 2.15 (P = 0.032)							
5 N-acetylcysteine 1800 mg daily							
Zheng 2014	482	0.1 (0.15)	482	0.13 (0.17)		100.0 %	-0.03 [-0.05, -0.01]
Subtotal (95% CI)	**482**		**482**			**100.0 %**	**-0.03 [-0.05, -0.01]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.91 (P = 0.0037)							
6 Carbocysteine							
Allegra 1996	223	0.07 (0.11)	218	0.11 (0.14)		25.6 %	-0.04 [-0.06, -0.02]
Grassi 1994	42	0.16 (0.29)	41	0.45 (0.43)		0.6 %	-0.29 [-0.45, -0.13]
Grillage 1985	54	0.1 (0)	55	0.12 (0)			Not estimable
Zheng 2008	353	0.08416 (0.094)	354	0.11 (0.094)		73.8 %	-0.03 [-0.04, -0.01]
Subtotal (95% CI)	**672**		**668**			**100.0 %**	**-0.03 [-0.04, -0.02]**
Heterogeneity: Chi^2 = 10.92, df = 2 (P = 0.004); I^2 =82%							
Test for overall effect: Z = 5.40 (P < 0.00001)							
7 Other mucolytic							
Bontognali 1991	30	0.7 (3.76)	30	1.27 (4.58)		0.0 %	-0.57 [-2.69, 1.55]
Castiglioni 1986	311	0.1 (0.21)	302	0.2 (0.29)		13.6 %	-0.10 [-0.14, -0.06]
Cremonini 1986	21	0.25 (0.23)	20	0.71 (0.29)		0.8 %	-0.46 [-0.62, -0.30]

(*Continued* . . .)

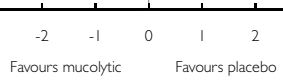
(. . . *Continued*)

Study or subgroup	Mucolytic N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Malerba 2004	115	0.06 (0.08)	119	0.07 (0.08)		52.2 %	-0.01 [-0.03, 0.01]
Meister 1999	122	0.06 (0.15)	124	0.1 (0.15)		15.6 %	-0.04 [-0.08, 0.00]
Moretti 2004	63	0.12 (0.14)	61	0.17 (0.17)		7.3 %	-0.05 [-0.10, 0.00]
Olivieri 1987	110	0.18 (0.31)	104	0.33 (0.41)		2.3 %	-0.15 [-0.25, -0.05]
Worth 2009	110	0.067 (0.136)	110	0.15 (0.24)		8.3 %	-0.08 [-0.13, -0.03]
Subtotal (95% CI)	**882**		**870**			**100.0 %**	**-0.04 [-0.06, -0.03]**

Heterogeneity: Chi^2 = 50.78, df = 7 (P<0.00001); I^2 =86%

Test for overall effect: Z = 5.68 (P < 0.00001)

Test for subgroup differences: Chi^2 = 75.85, df = 6 (P = 0.00), I^2 =92%



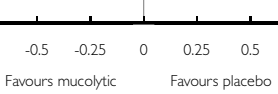
Analysis 1.6. Comparison 1 Mucolytic versus placebo, Outcome 6 Number of exacerbations per participant per month, by FEV1.

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

Comparison: 1 Mucolytic versus placebo

Outcome: 6 Number of exacerbations per participant per month, by FEV_1

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 Studies with mean $FEV_1 \leq$ 50% predicted							
McGavin 1985	72	0.42 (0.34)	76	0.52 (0.35)		0.4 %	-0.10 [-0.21, 0.01]
Olivieri 1987	110	0.18 (0.31)	104	0.33 (0.41)		0.5 %	-0.15 [-0.25, -0.05]
Zheng 2014	482	0.1 (0.15)	482	0.13 (0.17)		11.7 %	-0.03 [-0.05, -0.01]
Subtotal (95% CI)	**664**		**662**			**12.6 %**	**-0.04 [-0.06, -0.02]**
Heterogeneity: Chi^2 = 6.82, df = 2 (P = 0.03); I^2 =71%							
Test for overall effect: Z = 3.71 (P = 0.00021)							
2 Studies with mean FEV_1 > 50% predicted							
Allegra 1996	223	0.07 (0.11)	218	0.11 (0.14)		8.7 %	-0.04 [-0.06, -0.02]
Boman 1983	98	0.2 (0.27)	105	0.32 (0.3)		0.8 %	-0.12 [-0.20, -0.04]
Castiglioni 1986	311	0.1 (0.21)	302	0.2 (0.29)		3.0 %	-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)		8.7 %	-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]
Hansen 1994	59	0.11 (0.15)	70	0.16 (0.19)		1.4 %	-0.05 [-0.11, 0.01]
Malerba 2004	115	0.06 (0.08)	119	0.07 (0.08)		11.4 %	-0.01 [-0.03, 0.01]
Meister 1999	122	0.06 (0.15)	124	0.1 (0.15)		3.4 %	-0.04 [-0.08, 0.00]
Moretti 2004	63	0.12 (0.14)	61	0.17 (0.17)		1.6 %	-0.05 [-0.10, 0.00]
Nowak 1999	147	0.03 (0.06)	148	0.06 (0.12)		10.3 %	-0.03 [-0.05, -0.01]
Pela 1999	83	0.17 (0.18)	80	0.29 (0.32)		0.7 %	-0.12 [-0.20, -0.04]
Schermer 2009	96	0.08 (0.1)	96	0.06 (0.05)		9.6 %	0.02 [0.00, 0.04]
Tse 2013	58	0.08 (0.24)	62	0.14 (0.24)		0.7 %	-0.06 [-0.15, 0.03]
Worth 2009	110	0.067 (0.136)	110	0.15 (0.24)		1.8 %	-0.08 [-0.13, -0.03]
Zheng 2008	353	0.08416 (0.094)	354	0.11 (0.094)		25.0 %	-0.03 [-0.04, -0.01]
Subtotal (95% CI)	**2157**		**2177**			**87.4 %**	**-0.03 [-0.04, -0.02]**
Heterogeneity: Chi^2 = 91.39, df = 15 (P<0.00001); I^2 =84%							



(*Continued* . . .)

(. . . *Continued*)

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
Test for overall effect: Z = 7.47 (P < 0.00001)							
Total (95% CI)	**2821**		**2839**			**100.0 %**	**-0.03 [-0.04, -0.02]**
Heterogeneity: Chi^2 = 98.87, df = 18 (P<0.00001); I^2 =82%							
Test for overall effect: Z = 8.30 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 0.66, df = 1 (P = 0.41), I^2 =0.0%							

Analysis 1.7. Comparison 1 Mucolytic versus placebo, Outcome 7 Number of exacerbations per participant per month, no ICS.

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

Comparison: 1 Mucolytic versus placebo

Outcome: 7 Number of exacerbations per participant per month, no ICS

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 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							

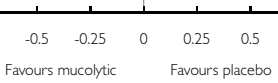
Analysis 1.8. Comparison 1 Mucolytic versus placebo, Outcome 8 Number of exacerbations per participant per month, by study duration.

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

Comparison: 1 Mucolytic versus placebo

Outcome: 8 Number of exacerbations per participant per month, by study duration

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 Duration ≤ 3 months							
Bontognali 1991	30	0.7 (3.76)	30	1.27 (4.58)		0.0 %	-0.57 [-2.69, 1.55]
Castiglioni 1986	311	0.1 (0.21)	302	0.2 (0.29)		2.7 %	-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]
Grassi 1994	42	0.16 (0.29)	41	0.45 (0.43)		0.2 %	-0.29 [-0.45, -0.13]
Jackson 1984	61	0.11 (0)	60	0.13 (0)			Not estimable
Subtotal (95% CI)	**465**		**453**			**3.1 %**	**-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 and < 12 months							
Grillage 1985	54	0.1 (0)	55	0.12 (0)			Not estimable
Allegra 1996	223	0.07 (0.11)	218	0.11 (0.14)		7.9 %	-0.04 [-0.06, -0.02]
Babolini 1980	254	0.13 (0.18)	241	0.33 (0.27)		2.6 %	-0.20 [-0.24, -0.16]
Boman 1983	98	0.2 (0.27)	105	0.32 (0.3)		0.7 %	-0.12 [-0.20, -0.04]
Borgia 1981	10	0.05 (0.08)	9	0.15 (0.17)		0.3 %	-0.10 [-0.22, 0.02]
Grassi 1976	35	0.14 (0.15)	34	0.27 (0.21)		0.6 %	-0.13 [-0.22, -0.04]
Hansen 1994	59	0.11 (0.15)	70	0.16 (0.19)		1.3 %	-0.05 [-0.11, 0.01]
McGavin 1985	72	0.42 (0.34)	76	0.52 (0.35)		0.4 %	-0.10 [-0.21, 0.01]
Meister 1986	90	0.15 (0.15)	91	0.2 (0.19)		1.8 %	-0.05 [-0.10, 0.00]
Meister 1999	122	0.06 (0.15)	124	0.1 (0.15)		3.1 %	-0.04 [-0.08, 0.00]
Moretti 2004	63	0.12 (0.14)	61	0.17 (0.17)		1.5 %	-0.05 [-0.10, 0.00]
Nowak 1999	147	0.03 (0.06)	148	0.06 (0.12)		9.4 %	-0.03 [-0.05, -0.01]
Olivieri 1987	110	0.18 (0.31)	104	0.33 (0.41)		0.5 %	-0.15 [-0.25, -0.05]
Parr 1987	243	0.18 (0.21)	210	0.21 (0.21)		2.9 %	-0.03 [-0.07, 0.01]
Pela 1999	83	0.17 (0.18)	80	0.29 (0.32)		0.7 %	-0.12 [-0.20, -0.04]
Rasmussen 1988	44	0.13 (0.21)	47	0.14 (0.19)		0.6 %	-0.01 [-0.09, 0.07]



(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Mucolytic N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Worth 2009	110	0.067 (0.136)	110	0.15 (0.24)		1.6 %	-0.08 [-0.13, -0.03]
Tse 2013	58	0.08 (0.24)	62	0.14 (0.24)		0.6 %	-0.06 [-0.15, 0.03]
Subtotal (95% CI)	**1875**		**1845**			**36.4 %**	**-0.06 [-0.07, -0.05]**
Heterogeneity: Chi^2 = 72.70, df = 16 (P<0.00001); I^2 =78%							
Test for overall effect: Z = 10.41 (P < 0.00001)							
3 Duration ≥ 12 months							
Malerba 2004	115	0.06 (0.08)	119	0.07 (0.08)		10.4 %	-0.01 [-0.03, 0.01]
Zheng 2008	353	0.08416 (0.094)	354	0.11 (0.094)		22.8 %	-0.03 [-0.04, -0.01]
Schermer 2009	96	0.08 (0.1)	96	0.06 (0.05)		8.7 %	0.02 [0.00, 0.04]
Zheng 2014	482	0.1 (0.15)	482	0.13 (0.17)		10.7 %	-0.03 [-0.05, -0.01]
Decramer 2005	256	0.1 (0.11)	267	0.11 (0.16)		8.0 %	-0.01 [-0.03, 0.01]
Subtotal (95% CI)	**1302**		**1318**			**60.6 %**	**-0.02 [-0.02, -0.01]**
Heterogeneity: Chi^2 = 15.42, df = 4 (P = 0.004); I^2 =74%							
Test for overall effect: Z = 3.71 (P = 0.00021)							
Total (95% CI)	**3642**		**3616**			**100.0 %**	**-0.03 [-0.04, -0.03]**
Heterogeneity: Chi^2 = 171.50, df = 25 (P<0.00001); I^2 =85%							
Test for overall effect: Z = 10.35 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 60.95, df = 2 (P = 0.00), I^2 =97%							

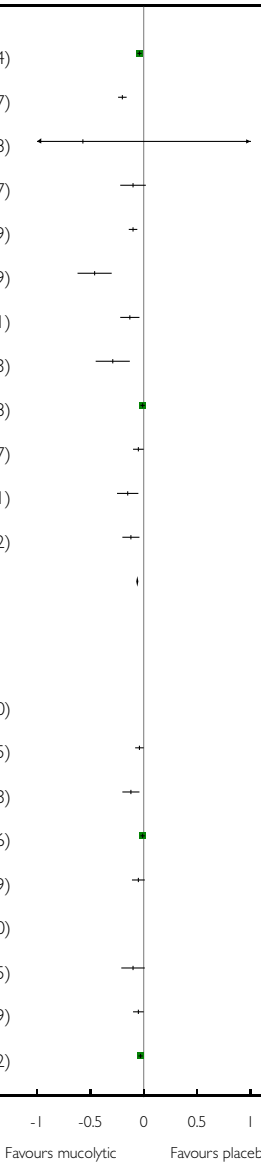
Analysis 1.9. Comparison 1 Mucolytic versus placebo, Outcome 9 Number of exacerbations per participant per month, by country.

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

Comparison: 1 Mucolytic versus placebo

Outcome: 9 Number of exacerbations per participant per month, by country

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 Italian							
Allegra 1996	223	0.07 (0.11)	218	0.11 (0.14)		7.9 %	-0.04 [-0.06, -0.02]
Babolini 1980	254	0.13 (0.18)	241	0.33 (0.27)		2.6 %	-0.20 [-0.24, -0.16]
Bontognali 1991	30	0.7 (3.76)	30	1.27 (4.58)		0.0 %	-0.57 [-2.69, 1.55]
Borgia 1981	10	0.05 (0.08)	9	0.15 (0.17)		0.3 %	-0.10 [-0.22, 0.02]
Castiglioni 1986	311	0.1 (0.21)	302	0.2 (0.29)		2.7 %	-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]
Grassi 1976	35	0.14 (0.15)	34	0.27 (0.21)		0.6 %	-0.13 [-0.22, -0.04]
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)		10.4 %	-0.01 [-0.03, 0.01]
Moretti 2004	63	0.12 (0.14)	61	0.17 (0.17)		1.5 %	-0.05 [-0.10, 0.00]
Olivieri 1987	110	0.18 (0.31)	104	0.33 (0.41)		0.5 %	-0.15 [-0.25, -0.05]
Pela 1999	83	0.17 (0.18)	80	0.29 (0.32)		0.7 %	-0.12 [-0.20, -0.04]
Subtotal (95% CI)	**1297**		**1259**			**27.5 %**	**-0.06 [-0.07, -0.05]**
Heterogeneity: Chi^2 = 115.59, df = 11 (P<0.00001); I^2 =90%							
Test for overall effect: Z = 9.49 (P < 0.00001)							
2 Non-Italian							
Grillage 1985	54	0.1 (0)	55	0.12 (0)			Not estimable
Meister 1999	122	0.06 (0.15)	124	0.1 (0.15)		3.1 %	-0.04 [-0.08, 0.00]
Boman 1983	98	0.2 (0.27)	105	0.32 (0.3)		0.7 %	-0.12 [-0.20, -0.04]
Decramer 2005	256	0.1 (0.11)	267	0.11 (0.16)		8.0 %	-0.01 [-0.03, 0.01]
Hansen 1994	59	0.11 (0.15)	70	0.16 (0.19)		1.3 %	-0.05 [-0.11, 0.01]
Jackson 1984	61	0.11 (0)	60	0.13 (0)			Not estimable
McGavin 1985	72	0.42 (0.34)	76	0.52 (0.35)		0.4 %	-0.10 [-0.21, 0.01]
Meister 1986	90	0.15 (0.15)	91	0.2 (0.19)		1.8 %	-0.05 [-0.10, 0.00]
Nowak 1999	147	0.03 (0.06)	148	0.06 (0.12)		9.4 %	-0.03 [-0.05, -0.01]



(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Mucolytic N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Parr 1987	243	0.18 (0.21)	210	0.21 (0.21)		2.9 %	-0.03 [-0.07, 0.01]
Rasmussen 1988	44	0.13 (0.21)	47	0.14 (0.19)		0.6 %	-0.01 [-0.09, 0.07]
Zheng 2008	353	0.08416 (0.094)	354	0.11 (0.094)		22.8 %	-0.03 [-0.04, -0.01]
Worth 2009	110	0.067 (0.136)	110	0.15 (0.24)		1.6 %	-0.08 [-0.13, -0.03]
Schermer 2009	96	0.08 (0.1)	96	0.06 (0.05)		8.7 %	0.02 [0.00, 0.04]
Zheng 2014	482	0.1 (0.15)	482	0.13 (0.17)		10.7 %	-0.03 [-0.05, -0.01]
Tse 2013	58	0.08 (0.24)	62	0.14 (0.24)		0.6 %	-0.06 [-0.15, 0.03]
Subtotal (95% CI)	**2345**		**2357**			**72.5 %**	**-0.03 [-0.03, -0.02]**
Heterogeneity: Chi^2 = 33.14, df = 13 (P = 0.002); I^2 =61%							
Test for overall effect: Z = 6.31 (P < 0.00001)							
Total (95% CI)	**3642**		**3616**			**100.0 %**	**-0.03 [-0.04, -0.03]**
Heterogeneity: Chi^2 = 171.50, df = 25 (P<0.00001); I^2 =85%							
Test for overall effect: Z = 10.35 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 22.77, df = 1 (P = 0.00), I^2 =96%							

Analysis 1.10. Comparison 1 Mucolytic versus placebo, Outcome 10 Number of exacerbations per participant per month, in participants included for history of exacerbation.

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

Comparison: 1 Mucolytic versus placebo

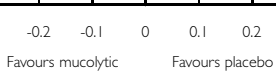
Outcome: 10 Number of exacerbations per participant per month, in participants included for history of exacerbation

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	223	0.07 (0.11)	218	0.11 (0.14)		9.6 %	-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]
Bontognali 1991	30	0.7 (3.76)	30	1.27 (4.58)		0.0 %	-0.57 [-2.69, 1.55]
Borgia 1981	10	0.05 (0.08)	9	0.15 (0.17)		0.4 %	-0.10 [-0.22, 0.02]
Decramer 2005	256	0.1 (0.11)	267	0.11 (0.16)		9.7 %	-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]
Grillage 1985	54	0.1 (0)	55	0.12 (0)			Not estimable
Hansen 1994	59	0.11 (0.15)	70	0.16 (0.19)		1.5 %	-0.05 [-0.11, 0.01]
Malerba 2004	115	0.06 (0.08)	119	0.07 (0.08)		12.7 %	-0.01 [-0.03, 0.01]
McGavin 1985	72	0.42 (0.34)	76	0.52 (0.35)		0.4 %	-0.10 [-0.21, 0.01]
Meister 1986	90	0.15 (0.15)	91	0.2 (0.19)		2.1 %	-0.05 [-0.10, 0.00]
Meister 1999	122	0.06 (0.15)	124	0.1 (0.15)		3.8 %	-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)		11.4 %	-0.03 [-0.05, -0.01]
Olivieri 1987	110	0.18 (0.31)	104	0.33 (0.41)		0.6 %	-0.15 [-0.25, -0.05]
Parr 1987	243	0.18 (0.21)	210	0.21 (0.21)		3.5 %	-0.03 [-0.07, 0.01]
Rasmussen 1988	44	0.13 (0.21)	47	0.14 (0.19)		0.8 %	-0.01 [-0.09, 0.07]
Zheng 2008	353	0.08416 (0.094)	354	0.11 (0.094)		27.7 %	-0.03 [-0.04, -0.01]
Zheng 2014	482	0.1 (0.15)	482	0.13 (0.17)		13.0 %	-0.03 [-0.05, -0.01]
Total (95% CI)	**2613**		**2611**			**100.0 %**	**-0.03 [-0.04, -0.02]**

Heterogeneity: Chi² = 33.54, df = 17 (P = 0.01); I² =49%

Test for overall effect: Z = 8.03 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 1.11. Comparison 1 Mucolytic versus placebo, Outcome 11 Days of disability per participant per month.

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

Comparison: 1 Mucolytic versus placebo

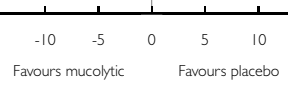
Outcome: 11 Days of disability per participant per month

Study or subgroup	Mucolytic		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
Allegra 1996	171	0.63 (1.23)	181	1.12 (1.61)		18.2 %	-0.49 [-0.79, -0.19]
Bontognali 1991	30	4.6 (3.76)	30	7.87 (4.58)		0.4 %	-3.27 [-5.39, -1.15]
Cegla 1988	86	0.59 (0)	87	0.86 (0)			Not estimable
Cremonini 1986	20	0.55 (0.75)	21	2.54 (2.25)		1.6 %	-1.99 [-3.01, -0.97]
McGavin 1985	72	0.96 (1.36)	76	1.02 (1.92)		5.7 %	-0.06 [-0.59, 0.47]
Meister 1986	90	1.4 (0)	91	2.95 (0)			Not estimable
Nowak 1999	147	0.35 (0)	148	0.76 (0)			Not estimable
Olivieri 1987	110	0.68 (1.16)	104	1.33 (1.68)		10.7 %	-0.65 [-1.04, -0.26]
Pela 1999	85	0.98 (0.75)	84	1.28 (1.9)		8.5 %	-0.30 [-0.74, 0.14]
Petty 1990	180	6.3 (0)	181	10.2 (0)			Not estimable
Rasmussen 1988	44	1.43 (2.87)	47	1.98 (3.78)		0.9 %	-0.55 [-1.92, 0.82]
Worth 2009	110	0.67 (1.82)	110	0.95 (1.48)		8.4 %	-0.28 [-0.72, 0.16]
Zheng 2014	482	1.23 (1.16)	482	1.6 (1.76)		45.7 %	-0.37 [-0.56, -0.18]
Total (95% CI)	**1627**		**1642**			**100.0 %**	**-0.43 [-0.56, -0.30]**

Heterogeneity: Chi^2 = 20.37, df = 8 (P = 0.01); I^2 =61%

Test for overall effect: Z = 6.59 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 1.12. Comparison 1 Mucolytic versus placebo, Outcome 12 Days on antibiotics per participant per month.

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

Comparison: 1 Mucolytic versus placebo

Outcome: 12 Days on antibiotics per participant 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 1.13. Comparison 1 Mucolytic versus placebo, Outcome 13 Health-related quality of life (total score St George Respiratory Questionnaire).

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

Comparison: 1 Mucolytic versus placebo

Outcome: 13 Health-related quality of life (total score St George Respiratory Questionnaire)

Study or subgroup	Mucolytic N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Decramer 2005	165	34.65 (16)	146	36.25 (15)		24.2 %	-1.60 [-5.05, 1.85]
Tse 2013	58	28.54 (17.5)	62	25.8 (17.3)		7.4 %	2.74 [-3.49, 8.97]
Worth 2009	110	34.5 (18.9)	110	41.3 (22.5)		9.5 %	-6.80 [-12.29, -1.31]
Zheng 2008	305	37.51 (21.39)	311	42.78 (22.91)		23.4 %	-5.27 [-8.77, -1.77]
Zheng 2014	482	40 (22.06)	482	41.5 (23)		35.5 %	-1.50 [-4.35, 1.35]
Total (95% CI)	**1120**		**1111**			**100.0 %**	**-2.60 [-4.29, -0.90]**

Heterogeneity: Chi^2 = 8.20, df = 4 (P = 0.08); I^2 =51%

Test for overall effect: Z = 3.01 (P = 0.0026)

Test for subgroup differences: Not applicable

Analysis 1.14. Comparison 1 Mucolytic versus placebo, Outcome 14 Hospitalisation during study period.

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

Comparison: 1 Mucolytic versus placebo

Outcome: 14 Hospitalisation during 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		44.7 %	0.79 [0.53, 1.18]
Moretti 2004	10/79	19/76		11.2 %	0.45 [0.20, 1.00]
Zheng 2014	33/495	36/495		30.3 %	0.91 [0.56, 1.49]
Tse 2013	26/58	45/62		13.8 %	0.32 [0.15, 0.66]
Total (95% CI)	**888**	**900**		**100.0 %**	**0.68 [0.52, 0.89]**

Total events: 124 (mucolytic), 169 (placebo)

Heterogeneity: Chi^2 = 7.07, df = 3 (P = 0.07); I^2 =58%

Test for overall effect: Z = 2.79 (P = 0.0053)

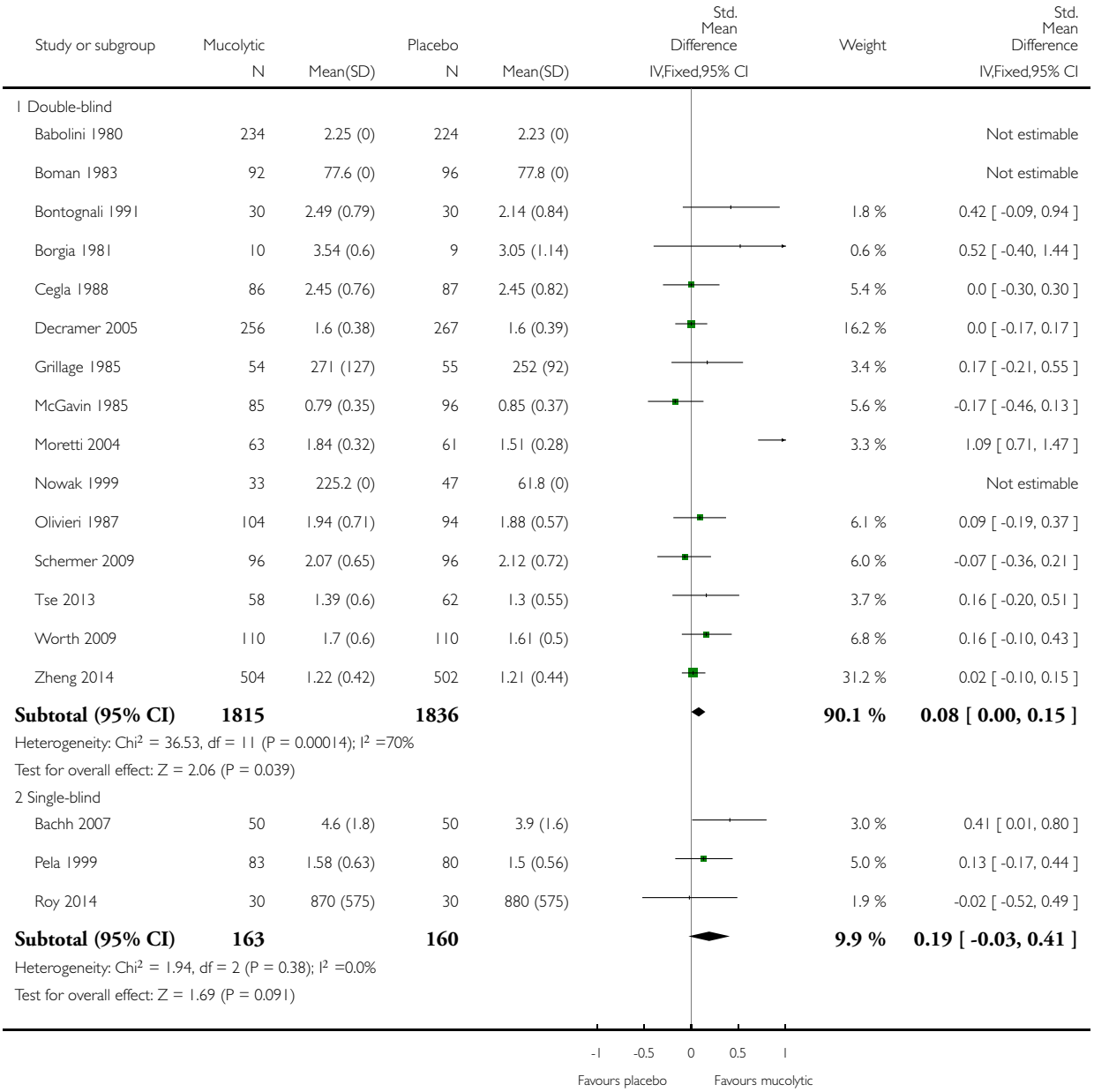
Test for subgroup differences: Not applicable

Analysis 1.15. Comparison 1 Mucolytic versus placebo, Outcome 15 FEV1 or % predicted FEV1 or PEFR at end of study.

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

Comparison: 1 Mucolytic versus placebo

Outcome: 15 FEV_1 or % predicted FEV_1 or PEFR at end of study



(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Mucolytic N	Mucolytic Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
Total (95% CI)	**1978**		**1996**		◆	**100.0 %**	**0.09 [0.02, 0.16]**
Heterogeneity: Chi² = 39.38, df = 14 (P = 0.00032); I² =64%							
Test for overall effect: Z = 2.49 (P = 0.013)							
Test for subgroup differences: Chi² = 0.91, df = 1 (P = 0.34), I² =0.0%							

-1 -0.5 0 0.5 1

Favours placebo Favours mucolytic

Analysis 1.16. Comparison 1 Mucolytic versus placebo, Outcome 16 FVC at end of study.

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

Comparison: 1 Mucolytic versus placebo

Outcome: 16 FVC at end of study

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
Babolini 1980	234	3.31 (0)	224	3.37 (0)			Not estimable
Bontognali 1991	30	3.5 (1)	30	3.07 (1.02)		0.3 %	0.43 [-0.08, 0.94]
Borgia 1981	10	4.58 (0.63)	9	4.58 (1.29)		0.1 %	0.0 [-0.93, 0.93]
Cegla 1988	86	3.48 (0.79)	87	3.48 (0.88)		1.2 %	0.0 [-0.25, 0.25]
McGavin 1985	85	1.89 (0.67)	96	1.89 (0.71)		1.9 %	0.0 [-0.20, 0.20]
Olivieri 1987	98	2.99 (0.77)	89	2.95 (0.74)		1.6 %	0.04 [-0.18, 0.26]
Schermer 2009	96	3.39 (1)	96	3.36 (1)		0.9 %	0.03 [-0.25, 0.31]
Tse 2013	58	2.64 (0.09)	62	2.58 (0.08)		81.2 %	0.06 [0.03, 0.09]
Worth 2009	110	2.36 (0.9)	110	2.22 (0.7)		1.7 %	0.14 [-0.07, 0.35]
Zheng 2014	504	2.47 (0.65)	502	2.46 (0.69)		11.0 %	0.01 [-0.07, 0.09]
Total (95% CI)	**1311**		**1305**			**100.0 %**	**0.05 [0.03, 0.08]**
Heterogeneity: Chi² = 4.45, df = 8 (P = 0.81); I² =0.0%							
Test for overall effect: Z = 3.87 (P = 0.00011)							
Test for subgroup differences: Not applicable							

-2 -1 0 1 2

Favours placebo Favours mucolytic

Analysis 1.17. Comparison 1 Mucolytic versus placebo, Outcome 17 Adverse effects.

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

Comparison: 1 Mucolytic versus placebo

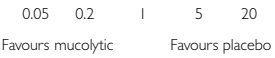
Outcome: 17 Adverse effects

Study or subgroup	Mucolytic n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Babolini 1980	23/371	41/373		7.5 %	0.54 [0.31, 0.91]
Boman 1983	44/127	43/132		5.4 %	1.10 [0.66, 1.84]
Jackson 1984	17/61	31/60		4.4 %	0.36 [0.17, 0.77]
McGavin 1985	20/85	15/96		2.1 %	1.66 [0.79, 3.50]
Grillage 1985	15/54	12/55		1.7 %	1.38 [0.58, 3.30]
Meister 1986	44/90	46/91		4.6 %	0.94 [0.52, 1.68]
Castiglioni 1986	84/339	105/334		15.6 %	0.72 [0.51, 1.01]
Olivieri 1987	29/121	24/119		3.6 %	1.25 [0.68, 2.30]
Cegla 1988	10/86	14/87		2.4 %	0.69 [0.29, 1.64]
Petty 1990	39/180	48/181		7.4 %	0.77 [0.47, 1.24]
Bontognali 1991	3/30	1/30		0.2 %	3.22 [0.32, 32.89]
Allegra 1996	16/223	31/218		5.7 %	0.47 [0.25, 0.88]
Pela 1999	6/85	3/84		0.6 %	2.05 [0.50, 8.48]
Nowak 1999	22/159	30/154		5.2 %	0.66 [0.36, 1.21]
Moretti 2004	14/63	19/61		2.9 %	0.63 [0.28, 1.41]
Bachh 2007	0/50	0/50			Not estimable
Zheng 2008	57/353	56/354		9.2 %	1.02 [0.69, 1.53]
Worth 2009	15/110	13/110		2.2 %	1.18 [0.53, 2.61]
Tse 2013	3/58	5/62		0.9 %	0.62 [0.14, 2.73]
Roy 2014	1/30	2/30		0.4 %	0.48 [0.04, 5.63]
Zheng 2014	146/495	130/495		18.0 %	1.17 [0.89, 1.55]

(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Mucolytic n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Total (95% CI)	**3170**	**3176**		**100.0 %**	**0.88 [0.78, 1.00]**
Total events: 608 (Mucolytic), 669 (Placebo)					
Heterogeneity: Chi^2 = 30.05, df = 19 (P = 0.05); I^2 =37%					
Test for overall effect: Z = 1.93 (P = 0.054)					
Test for subgroup differences: Not applicable					



Analysis 1.18. Comparison 1 Mucolytic versus placebo, Outcome 18 Death during study period.

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

Comparison: 1 Mucolytic versus placebo

Outcome: 18 Death during study period

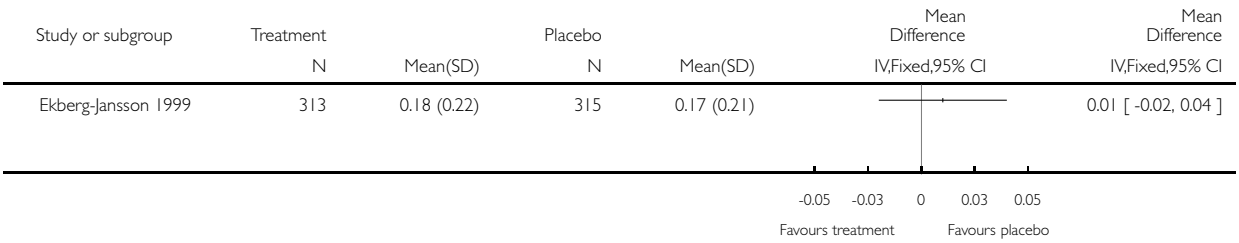
Study or subgroup	mucolytic n/N	placebo n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Jackson 1984	0/61	1/60		3.0 %	0.13 [0.00, 6.71]
Grillage 1985	1/54	1/55		6.0 %	1.02 [0.06, 16.50]
Pela 1999	0/84	1/85		3.0 %	0.14 [0.00, 6.90]
Decramer 2005	9/256	9/267		52.3 %	1.04 [0.41, 2.67]
Zheng 2008	0/353	0/354			Not estimable
Schermer 2009	1/96	3/96		11.8 %	0.36 [0.05, 2.61]
Tse 2013	2/58	1/62		8.9 %	2.11 [0.22, 20.71]
Zheng 2014	4/495	1/495		15.0 %	3.34 [0.58, 19.33]
Total (95% CI)	**1457**	**1474**		**100.0 %**	**1.03 [0.52, 2.03]**
Total events: 17 (mucolytic), 17 (placebo)					
Heterogeneity: Chi^2 = 5.24, df = 6 (P = 0.51); I^2 =0.0%					
Test for overall effect: Z = 0.09 (P = 0.93)					
Test for subgroup differences: Not applicable					

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

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

Comparison: 2 Systemic thiol donor versus placebo

Outcome: 1 Number of exacerbations per participant per month

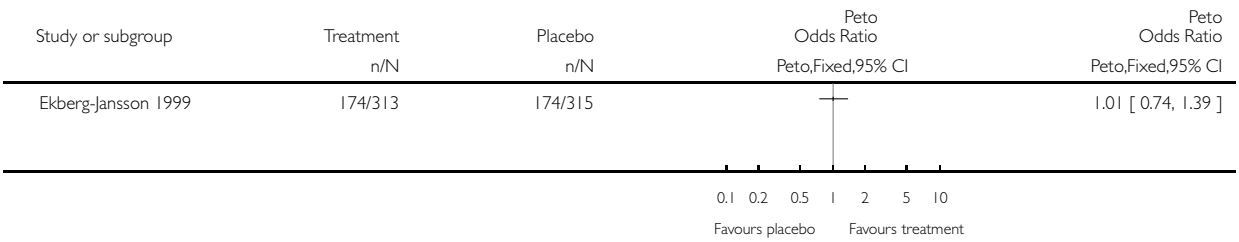


Analysis 2.2. Comparison 2 Systemic thiol donor versus placebo, Outcome 2 Participants with no exacerbations in the study period.

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

Comparison: 2 Systemic thiol donor versus placebo

Outcome: 2 Participants with no exacerbations in the study period



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

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

Comparison: 2 Systemic thiol donor versus placebo

Outcome: 3 Days of disability per participant per month

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

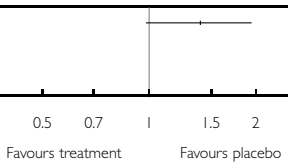
Analysis 2.4. Comparison 2 Systemic thiol donor versus placebo, Outcome 4 Adverse effects.

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

Comparison: 2 Systemic thiol donor versus placebo

Outcome: 4 Adverse effects

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



APPENDICES

Appendix 1. Search history

Years	Search result detail
All years to January 1998	We screened approximately 400 abstracts of papers identified by computer searches. After excluding studies that were clearly ineligible based on the abstract, we obtained the full text for 72 papers. 21 studies involved double-blind, placebo-controlled treatment with an oral mucolytic for at least 8 weeks. 3 were excluded because they did not provide 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 outcome measures of interest, and we could not obtain this information despite writing to study authors. 15 studies were included in the review
January 1998 to 1999	For the 1999 update, one further study was 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 participants with no exacerbations - an outcome measure that was added for the update. For this update, and until further clarification is obtained from study authors, we have assumed that error measurement reported in the paper of Olivieri 1987 is an SE rather than an 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 were retrieved; none were eligible
January 2003-Sept 2005	An update search conducted in 2005 yielded another 264 titles, of which 9 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 a further 2 titles were found with the COOPT study eligible
2008	Searches in 2008 yielded 20 titles, with 2 more original studies for inclusion (Bachh 2007; Zheng 2008)
May 2011	In 2011, 64 abstracts and papers were identified by the searches. Several reports were related to the PEACE study (Zheng 2008) and to the EQUALIFE study (Moretti 2004) already included in this review. Of 7 full texts reviewed, 4 proved eligible: 2 related 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 no data were available on outcomes in this review Furthermore, we were informed about studies of neltenexine, which is a mucolytic, and we considered the full texts of these, which were ineligible. Thus data from 2 new studies were added for the 2012 update

(*Continued*)

	(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 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, 8 abstracts and papers were identified. An abstract (Moretti 2011a) was added to 'Studies awaiting classification'
July 2014	A search in July 2014 using the terms below yielded 29 new references. (The full search strategy used in this update is provided in Appendix 3.) Full texts of studies that were possibly eligible were retrieved. The Moretti trial mentioned above was ineligible. Several studies had duplicate reports. A search was made of the bibliographies of eligible studies, as well as of online clinical trials. A duplicate paper on a trial already identified was found during a search for study author details. From these searches, 4 new eligible trials were identified for inclusion in this review (De Backer 2013; Roy 2014; Tse 2013; Zheng 2014). We wrote to Dr De Backer to request additional information on the secondary outcomes of SGRQ and spirometry alluded to in their paper, with no response. Dr Zheng provided further information on several outcomes (Zheng 2014)

Appendix 2. Sources and search methods for the Cochrane Airways Group Specialised Register (CAGR)

Electronic searches: core databases

Database	Frequency of search
CENTRAL	Monthly
MEDLINE (Ovid)	Weekly
EMBASE (Ovid)	Weekly
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

Appendix 3. Search strategy to identify relevant trials from the CAGR

Search platform: Cochrane Register of Studies (CRS)

#1 MeSH DESCRIPTOR Pulmonary Disease, Chronic Obstructive Explode All
#2 MeSH DESCRIPTOR Bronchitis, Chronic
#3 (obstruct*) near3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)
#4 COPD:MISC1
#5 (COPD OR COAD OR COBD):TI,AB,KW
#6 #1 OR #2 OR #3 OR #4 OR #5
#7 MeSH DESCRIPTOR Expectorants
#8 mucolytic*
#9 mucociliary* NEXT clearance*
#10 mucoactive
#11 *acetylcysteine
#12 bromhexine
#13 *carboxymethylcysteine
#14 ambroxol
#15 sobrerol
#16 “iodinated glycerol”
#17 isobutyrylcysteine
#18 myrtol
#19 NAC:ti,ab
#20 methylcysteine
#21 carbocysteine
#22 erdosteine
#23 strepronin*
#24 gelsolin
#25 mesna*
#26 cineole
#27 neltenexine
#28 eucalyptus
#29 #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28
#30 #6 and #29
[Note: in search line #4, MISC1 denotes the field in which the reference has been coded for condition, in this case, COPD]

WHAT'S NEW

Last assessed as up-to-date: 3 July 2014.

Date	Event	Description
3 July 2014	New search has been performed	New literature search

(*Continued*)

3 July 2014	New citation required but conclusions have not changed	• Change in review authors • Inclusion of 4 new studies, all of NAC vs placebo (De Backer 2013; Roy 2014; Tse 2013; Zheng 2014) • Addition of an analysis of studies lasting 12 months or longer • Addition to subgroup analysis of NAC at higher doses (1200 mg/d and 1800 mg/d) • For primary outcomes, minimal changes - all heading towards null effect, despite increased doses of NAC ○ Slightly reduced likelihood of no exacerbations during study period ○ Slightly reduced effect size for exacerbation rate • Addition of evidence of 'lack of effect' for all secondary outcomes • Addition of 'Summary of findings' table • Updated versions of 'Risk of bias' tables

HISTORY

Protocol first published: Issue 2, 1996

Review first published: Issue 4, 1998

Date	Event	Description
5 July 2012	New citation required and conclusions have changed	Conclusions similar, although smaller beneficial effects of mucolytics on exacerbations noted in more recent trials than in earlier trials
5 July 2012	New search has been performed	2 new studies (Worth 2009 (cineole) and Schermer 2009 (N-acetylcysteine (NAC))) included. Data from these studies and from Decramer 2005 included in a new analysis for SGRQ (St George Respiratory Questionnaire). 'Summary of findings' table added. Third review author (CC) added to the review. Potentially eligible abstract added to Studies awaiting classification
1 November 2008	New citation required but conclusions have not changed	Review updated to take account of 2 new studies
15 September 2008	New search has been performed	Search rerun
8 August 2008	Amended	Converted to new review format

(*Continued*)

10 March 2006	New citation required and conclusions have changed	2005: repeated search, performed full update. Three new studies, including 3-year BRONCHUS study of 600 mg NAC, included. Smaller effect size of all mucolytics combined than previously. Reasons for this discussed In the BRONCHUS study, significant effect of NAC on exacerbations noted among participants not using inhaled corticosteroids. New comparison added to address this Other new comparisons added: hospitalisations, deaths Otherwise, findings much the same as previously
1 August 2002	New search has been performed	2002: no new studies found despite use of wider search strategy. Discussion 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 now included Data and conclusions same as in 1999
31 August 1999	New search has been performed	1999: 2 studies in patients with COPD now included in the review, hence the title change. Data on 2 other agents - myrtol and the thiol donor N-isobutyrylcysteine - also included. Eight additional studies and several new analyses included Correction made to reviewers' conclusions on the effects of mucolytics on the secondary endpoint of lung function. Our extracteddata checked against original data and confirmed as correct. Small standard deviations in the Olivieri study noted; possibility that study authors reported standard errors. P values quoted in study analysis compatible with this conclusion. Until clarification, this trial removed from analysis. No significant change in lung function noted in data analysis (previously interpreted as favouring placebo). Changes made to relevant parts of Abstract, Results (Lung Function) and Discussion sections No change to overall conclusions of this review with respect to primary endpoint of exacerbation frequency and days of disability ('sick days'). High level of heterogeneity in the size of this effect between trials unclear; possibility that length of study is the cause of this

(*Continued*)

		should be examined in a future version of this review For adverse effects, Parr and Rasmussen data taken out of meta-analysis and reported instead in text because event rates in these studies exceeded numbers in treatment groups. RevMan unable to manage dichotomous data when event rate exceeds 1. Possibility that adverse effects may be less frequent in the mucolytic-treated group as suggested by meta-analysis. In large study by Parr (n = 526), mean of 4.9 adverse effects reported per participant in the mucolytic group vs 4.5 adverse effects per participant in the placebo group. Therefore, no changes made to our original conclusion and no differences 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. He has assisted with analysis, interpretation, data-checking and write-up of the 2012 and 2014/15 updates. Dr Jimmy Chong assisted with determining study eligibility, checking data and writing up the 2012 and 2014/15 updates.

Rebecca Normansell was the Editor for this review and commented critically on the review.

DECLARATIONS OF INTEREST

No financial support was received for this review, and the review authors have reported no conflict of interest.

SOURCES OF SUPPORT

Internal sources

- No support received, Other.

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 for Systematic Reviews of Interventions. The protocol and initial review versions used Jadad scores to assess trial quality. We have updated the 'Risk of bias' assessment to use the latest version of the Cochrane 'Risk of bias' tool.

Additional outcomes were added for updates from 2006 to 2012.

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

Double-blinding was not an inclusion criterion.

INDEX TERMS

Medical Subject Headings (MeSH)

Bronchitis [*drug therapy; prevention & control]; Chronic Disease; Disease Progression; Expectorants [adverse effects; *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