Mucolytics for acute exacerbations of chronic obstructive pulmonary disease: a meta-analysis

Efthymia Papadopoulou [1], Jan Hansel [2], Zsofia Lazar [3], Konstantinos Kostikas [4], Stavros Tryfon [1], Jørgen Vestbo [5,6] and Alexander G. Mathioudakis [5,6]

[1]Pulmonology Department, General Hospital of Thessaloniki 'G. Papanikolaou', Thessaloniki, Greece. [2]North West School of Intensive Care Medicine, Health Education England – North West, Manchester, UK. [3]Department of Pulmonology, Semmelweis University, Budapest, Hungary. [4]Respiratory Medicine Department, University of Ioannina School of Medicine, Ioannina, Greece. [5]Division of Immunology, Immunity to Infection and Respiratory Medicine, School of Biological Sciences, The University of Manchester, Manchester, UK. [6]North West Lung Centre, Wythenshawe Hospital, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK.

Corresponding author: Alexander G. Mathioudakis (alexander.mathioudakis@manchester.ac.uk)

Shareable abstract (@ERSpublications)
A meta-analysis of 24 RCTs (N=2192) demonstrated with moderate certainty that mucolytics can improve treatment success rate by 37% and significantly improve symptoms in COPD exacerbations #AECOPD. There were no safety signals. https://bit.ly/3RwTzlU

Cite this article as: Papadopoulou E, Hansel J, Lazar Z, *et al*. Mucolytics for acute exacerbations of chronic obstructive pulmonary disease: a meta-analysis. *Eur Respir Rev* 2023; 32: 220141 [DOI: 10.1183/16000617.0141-2022].

Received: 27 July 2022
Accepted: 27 Sept 2022

Abstract

This meta-analysis explored the safety and effectiveness of mucolytics as an add-on treatment for chronic obstructive pulmonary disease (COPD) exacerbations. Based on a pre-registered protocol and following Cochrane methods, we systematically searched for relevant randomised or quasi-randomised controlled trials (RCTs). We used the Risk of Bias v2 tool for appraising the studies and performed random-effect meta-analyses when appropriate. We assessed certainty of evidence using GRADE. This meta-analysis included 24 RCTs involving 2192 patients with COPD exacerbations, entailing at least some concerns of methodological bias. We demonstrated with moderate certainty that mucolytics increase the rate of treatment success (relative risk 1.37, 95% CI 1.08–1.73, n=383), while they also exert benefits on overall symptom scores (standardised mean difference 0.86, 95% CI 0.63–1.09, n=316), presence of cough at follow-up (relative risk 1.93, 95% CI 1.15–3.23) and ease of expectoration (relative risk 2.94, 95% CI 1.68–5.12). Furthermore, low or very low certainty evidence suggests mucolytics may also reduce future risk of exacerbations and improve health-related quality of life, but do not impact on breathlessness, length of hospital stay, indication for higher level of care or serious adverse events. Overall, mucolytics could be considered for COPD exacerbation management. These findings should be validated in further, rigorous RCTs.

Introduction

Chronic obstructive pulmonary disease (COPD), the third leading cause of death globally, affects more than 300 million people worldwide [1, 2]. On average, COPD patients suffer from 0.5–3.5 exacerbations per year, that aggravate health status, quality of life and healthcare burden [3, 4]. Notably, COPD exacerbations, especially those with prolonged duration or incomplete recovery, precipitate unfavourable disease progression, which highlights the significance of their appropriate, rigorous management [5].

COPD exacerbations are characterised by substantial heterogeneity in their aetiology, clinical manifestations and underlying pathophysiological pathways, warranting a personalised approach to their management [6]. This is not yet fully realised in clinical practice, since their pharmacotherapy remains suboptimal, unchanged for decades, generic and mainly based on the administration of bronchodilators, antimicrobials and/or systemic corticosteroids [7]. The treatable traits theory inaugurates a patient-specific paradigm targeting clinically relevant, identifiable and modifiable features, and offers an effective, clinically practical methodology for personalising the management of airway diseases, including

exacerbations [8–10]. For instance, decompensated type 2 respiratory failure represents the most established trait, which is consistently treated with noninvasive ventilation [11]. Bacterial infections and airway eosinophilic inflammation are increasingly targeted with biomarker-guided administration of antimicrobials or systemic corticosteroids, respectively [12–14].

Hypersecretion of mucus with increased viscosity represents another key treatable trait both during stable disease and acute exacerbations. It is burdensome to patients and associated with unfavourable outcomes [15] and disease progression [16]. Mucolytics regulate mucus viscoelastic properties, mostly by altering the degree of crosslinks and molecular interactions within mucin polymers, thereby potentiating mucociliary clearance and promoting sputum expectoration [17]. They are commonly prescribed in mucus hypersecretory conditions, such as respiratory tract infections or cystic fibrosis, and often for patients with COPD, in view of the mucus hypersecretion and ciliary dysfunction [18]. Furthermore, some possess antioxidant properties and exert anti-inflammatory or immunomodulatory effects, which could also benefit this patient group [17]. When administered in a stable disease state, various mucolytics, such as N-acetylcysteine, carbocysteine, erdosteine and ambroxol, have shown effectiveness in preventing COPD exacerbations and, perhaps, hospitalisation due to exacerbation [19]. Nevertheless, in the absence of conclusive evidence on their effectiveness in the management of exacerbations, there is no consensus around their use in clinical practice.

This systematic review sought to synthesise and appraise all available evidence from randomised controlled trials (RCTs) around the safety and clinical effectiveness of mucolytics as an add-on treatment to the standard care of COPD exacerbations.

Materials and methods

This systematic review and meta-analysis is based on a protocol that was prospectively registered with PROSPERO (ID: CRD42022314958) [20] and follows the methodology recommended by the Cochrane collaboration [21] and the Grading of Recommendation, Assessment, Development and Evaluation (GRADE) working group [22]. The present report adheres to the PRISMA statement [23].

Eligibility criteria

Randomised and quasi-randomised controlled trials assessing the clinical safety and effectiveness of mucolytics for COPD exacerbations were considered eligible. We included adult patients presenting with a clinical diagnosis of a moderate or severe COPD exacerbation. We considered eligible any pharmacological intervention primarily aiming to dissolve thick sputum that might have been administered *via* any route, in addition to usual care. In cases of inhaled mucolytics, normal saline was considered an acceptable placebo control. We excluded trials that recruited patients in the intensive care unit (ICU, those that focused on patients where COPD exacerbation was not the primary cause of their symptoms (*e.g.* decompensated heart failure and pneumonia) or assessed long-term administration of mucolytics during stable COPD.

Outcome measures

We assessed all the outcomes included in the European Respiratory Society (ERS) COPD exacerbations core outcome set [24] and additional secondary outcomes relevant to the intervention (details in supplementary table A1). The primary outcomes comprised: 1) patient-reported symptoms, preferentially assessed using standardised tools (*e.g.* the modified Medical Research Council dyspnoea scale), 2) treatment success [25], defined as a dichotomous measure of the overall outcome of the exacerbation that may be based on the judgement of a clinician and/or assessment of symptoms, signs and/or laboratory findings. Secondary outcomes comprised: mortality, indication for higher level of care (admission to hospital or ICU for the presenting exacerbation), hospitalisation duration, levels of oxygen and carbon dioxide in the arterial blood, health-related quality of life, activities of daily living, worsening of symptoms after initial treatment, disease progression assessed by pulmonary function tests, future exacerbations and future hospital admissions, serious adverse events, development of pneumonia, treatment adherence, overall microbiological outcome, and sputum characteristics (*i.e.* viscosity, volume and purulence).

Search strategy, study selection and data abstraction

Using a structured search strategy (see supplementary appendix), on 20 March 2022 we searched MEDLINE/PubMed, the Cochrane Central Register of Controlled Trials, the Cochrane Airways Trials Register, the World Health Organization International Clinical Trials Registry Platform and the conference proceedings of the ERS, American Thoracic Society and Asian Pacific Society of Respirology. The reference lists of all relevant studies were further perused. There were no language or time restrictions. Two authors independently assessed all identified studies for eligibility at title/abstract level, proceeding to

full-text evaluation of all potentially eligible studies. Relevant data around the trial design, participant baseline characteristics, interventions and outcomes of interest were extracted in a structured and piloted Excel spreadsheet by two authors independently. Any disagreements were resolved through discussion or adjudication by a third reviewer.

Risk of bias and certainty of evidence assessment

The Cochrane Risk of Bias Tool v2 was used for assessing risk of bias at the study level [26, 27]. Moreover, certainty of the body of evidence per outcome was evaluated following GRADE methodology and taking into consideration the risk of bias, imprecision, inconsistency, indirectness and publication bias. We used a minimally contextualised approach for assessing GRADE. This approach focuses on assessing the presence rather than the magnitude of a potential treatment effect. We intended to use funnel plots for assessing publication bias in cases of meta-analyses involving at least 10 studies, but none of the meta-analyses fulfilled this criterion. The certainty was termed as "high", "moderate", "low" or "very low" according to GRADE [28].

Data synthesis

In anticipation of significant clinical and methodological heterogeneity, we performed random effect meta-analysis, using Review Manager 5.4.1 (Cochrane). Relative risks and mean differences (MDs), along with their 95% confidence intervals (95% CI), were calculated as effect estimates for dichotomous and continuous data, respectively. We used standardised mean differences (SMDs) to pool data from different scales/tools assessing the same outcome. SMD is used for conducting meta-analyses of various instruments assessing the same outcome (*e.g.* quality of life measured by different questionnaires). For calculating the SMD, the size of the intervention effect in each study is divided by the corresponding standard deviation. Heterogeneity was evaluated using the I^2 statistic and significant heterogeneity was explored *via* pre-specified subgroup analyses. We present narratively and in a tabulated format results of the included studies that were not reported in a format that could be included in the meta-analyses. All outcomes were assessed during treatment (we preferably captured measurements from the third to fifth treatment day), post-treatment (depending on the regimen) and long-term (>3 weeks) follow-up timepoints.

Sensitivity and subgroup analyses

For subgroup analyses, we intended to classify the trials according to exacerbation aetiology and severity, type or dosage of the mucolytics administered, and recruitment of patients with increased sputum viscosity or sputum volume.

Sensitivity analyses were performed using the fixed-effect model. We also intended to conduct a further sensitivity analysis only considering studies at a low risk of bias, but none of the included studies fulfilled this criterion.

Results

Study selection and baseline characteristics

The study selection process is depicted in the PRISMA flowchart (supplementary figure A1). 24 complete trials fulfilled the eligibility criteria totalling 2192 participants. Table 1 and supplementary table A2 present the characteristics of the included studies. Most trials were conducted in an inpatient clinical setting, with follow-up ranging from 7 days to 6 months. Patients with infective exacerbations were enrolled in seven trials [29–35], six of which only included patients with confirmed presence of bacteria in sputum cultures [30–35]. Another trial [36] recruited only patients receiving noninvasive ventilation. We did not identify significant baseline imbalances across the treatment arms of the included studies, although 10 studies only provided limited relevant information.

The most commonly administered mucolytic was N-acetylcysteine (10 trials), followed by ambroxol (n=5), erdosteine (n=5) and bromhexine (n=2), whereas hypertonic saline and high molecular weight hyaluronan were assessed in one trial each. Mucolytics were usually administered orally, but inhaled [36, 37–39] and intravenous [40, 41] routes were also used. The median treatment duration was 10 days, generally ranging between 7 and 30 days across the trials, but was limited to only 24 h in one [38].

Most studies were double blinded (n=14), and some were single blinded (n=5), while five studies did not report on blinding. Adherence to treatment was not quantified in any trial, but patient withdrawal was significant, up to 24% for the control group in one study [42], up to 22.5% for the mucolytic group in another [43] and reaching more than a 10% difference between treatment arms in two trials, with higher occurrence in the mucolytics groups [43, 44]. Unfortunately, most of these trials did not describe the reasons for withdrawal.

https://doi.org/10.1183/16000617.0141-2022

TABLE 1 Baseline characteristics of the included randomised controlled trials (RCTs)

Study	Study design, clinical setting, follow-up	N	Withdrawal (M/C)	Mean (SD) age, years, males, %	Inclusion diagnosis	Sputum at presentation	Treatment regimen
Ansari *et al.* [42]	RCT NR, inpatient, ⩾7 days	50	4/6	46.2 (10.7) 65.0%	Clinical AECOPD diagnosis with spirometric airflow obstruction	NR	NAC 1200 mg *p.o.* (twice daily), ⩾7 days *versus* standard treatment
Aytemur *et al.* [53]	RCT DB, inpatient, 6 months	42	1/3	69 (8.8) 92.1%	AECOPD with previous spirometry confirmation	Increased volume (>50 mL·day^{-1})	NAC 600 mg *p.o.* (three times daily), 30 days *versus* placebo
Bisetti *et al.* [52]	RCT DB, inpatient, 7 days	28	0/1	62.3 (NR) 67.9%	Clinical AECOPD diagnosis Background: chronic bronchitis	Mucopurulent	Erdosteine 600 mg *p.o.* (twice daily), 7 days *versus* placebo
Black *et al.* [54]	RCT DB, inpatient, 7 days	50	0/0	73.3 (8) 60.0%	AECOPD with spirometric airflow obstruction admitted for ⩽24 h	Mostly increased volume	NAC 600 mg *p.o.* (twice daily), ⩽7 days *versus* placebo
Brocard *et al.* [29]	RCT DB, NR, 10 days	95	NR	NR	Acute infective exacerbation Background: chronic bronchitis	NR	NAC 600 mg *p.o.* (three times daily) 10 days *versus* placebo
El Hafiz *et al.* [55]	RCT DB, inpatient, >10 days	45	0/0	59 (7.5) 100%	AECOPD with airflow obstruction in spirometry GOLD criteria fulfilment	NR	NAC 600 mg *p.o.* (three times daily), NAC 1200 mg *p.o.* (three times daily), 10 days *versus* standard treatment
Galdi *et al.* [36]	RCT DB, inpatient, NR	41	2/4	75.8 (9.4) 34.1%	AECOPD requiring NIPPV Previous diagnosis of COPD	NR	Neb high molecular weight hyaluronan 0.3% 5 mL saline (twice daily) during NIPPV *versus* placebo
Jahnz-Rózyk *et al.* [37]	RCT DB, inpatient, NR	30	0/0	70.5 (6.9) 43.3%	Clinical AECOPD diagnosis Background: chronic bronchitis	NR	Neb ambroxol 30 mg (twice daily), up to clinical and spirometric improvement *versus* placebo
Langlands *et al.* [44]	RCT DB, inpatient, 20 days	31	3/1	NR 81.5%	AECOPD based on MRC criteria Background: chronic bronchitis	Mucoid	Bromhexine 24 mg *p.o.* (three times daily), 14 days *versus* placebo
Li *et al.* [40]	RCT NR, inpatient, 10 days	60	6/4	68.1 (8.8) 62%	Chinese medicine syndrome of retention of phlegm and heat in Fei with airflow obstruction in spirometry Onset ⩽1 week	NR	Ambroxol 30 mg *i.v.* (twice daily), 10 days *versus* standard treatment
Maesen *et al.* [30]	RCT SB, inpatient, 17 days	22	NR	NR	Infective AECOPD Background: chronic bronchitis	Increased purulence	Bromhexine 72 mg (three times daily), 10 days *versus* placebo
Marchioni *et al.* [31]	RCT DB, NR, 11 days	237	6/5	64.1 (10.7) 76.4%	Infective, clinical AECOPD Background: chronic bronchitis	NR	Erdosteine 600 mg *p.o.* (twice daily), 7–10 days *versus* placebo
Mohanty *et al.* [50]	RCT DB, NR, NR	240	40 total	NR, NR	Clinical AECOPD diagnosis Background: chronic bronchitis	NR	Erdosteine 600 mg *p.o.*, NR *versus* placebo
Moretti *et al.* [48, 49]	RCT SB, inpatient, 60 days	15	0/0	69.6 (5.6) NR	Clinical AECOPD diagnosis Hospitalisation ⩽48 h from symptom onset	NR	Erdosteine 900 mg (three times daily), 10 days *versus* placebo
Moretti *et al.* [46, 56]	RCT SB, inpatient, 60 days	40	0/0	70.7 (5.8) 82.5%	Clinical AECOPD diagnosis with onset ⩽24 h	Increased volume and purulence	Erdosteine 900 mg *p.o.* (three times daily), 10 days *versus* standard treatment
Paganin *et al.* [32]	RCT NR, NR, >10 days	24	4 (total)	61.5 (7.4) 79.2%	Infective, clinical AECOPD diagnosis with airflow limitation	Increased purulence	Ambroxol 90 mg *p.o.* (three times daily), 10 days *versus* standard treatment

Continued

https://doi.org/10.1183/16000617.0141-2022

TABLE 1 Continued

Study	Study design, clinical setting, follow-up	N	Withdrawal (M/C)	Mean (SD) age, years, males, %	Inclusion diagnosis	Sputum at presentation	Treatment regimen
Patel *et al.* [38]	RCT SB, inpatient, 30 days	70	9/0	61.2 (9.3) 49.2%	AECOPD	NR	Neb hypertonic saline 3.00% (every 6 h and as needed), 24 h *versus* neb normal saline 0.9%
Peralta *et al.* [33]	RCT DB, NR, 10 days	24	1 (total)	60 (8.4) NR	Infective, clinical AECOPD Background: chronic bronchitis	Increased purulence	Ambroxol 90 mg *p.o.* (three times daily), 10 days *versus* standard treatment
Reichenberger *et al.* [34]	RCT NR, NR, 21 days	24	NR	66 (10) 66.7%	Infective clinical AECOPD Background: chronic bronchitis	NR	NAC 1200 mg (twice daily), 21 days *versus* standard treatment
Ren *et al.* [39]	Q-RCT SB, inpatient, NR	78	0	80.8 (4.4) 62.8%	Clinical AECOPD diagnosis, according to the Respiratory Branch of the Chinese Medical Association	NR	Inh NAC 600 mg (twice daily), NR *versus* inh normal saline (6 mL)
Ricevuti *et al.* [35]	RCT DB, NR, 8 days	30	0	51.5 (NR) 46.7%	Infective, clinical AECOPD Background: chronic bronchitis	Increased viscosity and volume	Erythromycin-propionate-N-acetylcysteinate *p.o.* (three times daily), 7 days *versus* erythromycin stearate
Study 7171L01 [45]	RCT DB, NR, 30 days	714	18.21/17	NR NR	Anthonisen's criteria for AECOPD and BCSS ⩾5 ATS/ERS criteria for COPD (documentation ⩽1 year)	NR	N-Acetylcysteine 1200 mg, 600 mg *p.o.* (once), 10 days *versus* placebo
Zhang *et al.* [41]	RCT NR, NR, NR	80	NR	NR NR	AECOPD	NR	Ambroxol 60 mg *i.v.* (twice daily), NR *versus* standard treatment
Zuin *et al.* [51]	RCT DB, outpatient, 10 days	122	0.1/1	66.7 (12.4) 57.4%	Clinical AECOPD diagnosi	NR	NAC 600 mg *p.o.* (once and once placebo), 1200 mg *p.o.* (twice daily), 10 days *versus* placebo (twice daily)

AECOPD: acute exacerbation of chronic obstructive pulmonary disease; ATS: American Thoracic Society; BCSS: Breathlessness, Cough and Sputum Scale; C: control group; DB: double-blinded; ERS: European Respiratory Society; GOLD: Global Initiative for Chronic Obstructive Lung Disease; inh: inhaled; *i.v.*: intravenous; M: mucolytic group; MRC: Medical Research Council; N: number of patients; NAC: N-acetylcysteine; neb: nebulised; NIPPV: noninvasive positive pressure ventilation; NR: not reported; *p.o.*: *per os*; Q-RCT: quasi-randomised controlled trial; SB: single-blinded; SD: standard deviation.

Acceptable concurrent treatments included bronchodilators, inhaled corticosteroids, systemic corticosteroids, antimicrobials and/or methylxanthines, with or without oxygen supplementation, whereas one study only included patients receiving noninvasive positive-pressure ventilation [36]. In two studies where administration of the mucolytic was *via* inhalation, the control group received normal saline as an inhaled placebo [38, 39]. Concurrent chest physiotherapy to facilitate mucus expectoration was only reported in one trial [29].

Risk of bias assessment

All studies entailed some concerns or high risk of bias, mainly due to unclear allocation sequence, per-protocol analysis, utilisation of nonvalidated scores in outcome measurements and selection bias (figure 1 and supplementary figure A1).

Meta-analyses

There was significant variability in the instruments used to assess the selected outcomes across the included studies. Moreover, information required for including results in the meta-analyses was often missing and, as a result, we were not able to pool all available data. Details of all relevant findings reported in the included trials are presented in supplementary table A3. Our meta-analyses are presented in figure 2 and supplementary figure A2. GRADE evidence profiles and detailed judgements for all clinically relevant outcomes are summarised in table 2.

Treatment success, defined as resolution or significant clinical, with or without laboratory, improvement, was assessed in four trials totalling 383 participants. Mucolytics significantly improved treatment success evaluated upon treatment completion (relative risk 1.37, 95% CI 1.08–1.73, I^2=63%, moderate certainty). Two of these studies, totalling 253 of the 383 participants, included in this meta-analysis were double blinded [31, 52]. Marchioni *et al.* [31] defined treatment success as resolution of symptoms as assessed by a physician, while Li *et al.* [40] required resolution or significant improvement of the symptoms, signs and laboratory findings. The definition of treatment success was not adequately described by Bisetti *et al.* [52] and Zhang *et al.* [41]. Two of the studies also assessed treatment failure (relative risk 0.81, 95% CI 0.21–3.06, I^2=0%, 287 participants, low certainty) [31, 40].

Patient-reported symptoms were addressed in 16 studies involving 1741 patients by means of composite scores, or by assessing treatment effects or specific symptoms. Of these, five tested composite symptom scores, evaluating breathlessness, cough and sputum expectoration, with or without fever [31, 40, 45–49]. Heterogeneous instruments were used for assessing symptom scores and for this reason we conducted meta-analyses using SMDs. Mucolytics were associated with better post-treatment overall symptom scores compared to controls (SMD 0.86, 95% CI 0.63–1.09, I^2=0%, three trials with 316 participants). One trial that assessed change from pre-treatment in composite symptom scores revealed significant improvement with mucolytics compared to control (SMD 0.80, 95% CI 0.22–1.38, one trial with 50 participants) [40]. Finally, Mohanty *et al.* [50] reported a significantly higher percentage of participants with improved symptoms compared to pre-treatment in the mucolytics group but not in the control group (relative risk 1.18, 95% CI 1.07–1.31, 200 participants). Early treatment response at day 4–5 was explored in one trial that favoured the mucolytics group (MD 1.50, 95% CI 0.85–2.15, 226 participants) [31]. Overall, we found moderate-certainty evidence suggesting that mucolytics improve overall symptom scores.

Eight studies explored the impact of mucolytics on breathlessness, mostly using nonvalidated scores. An RCT including 226 participants suggested that mucolytics can improve breathlessness compared to control [31], but this finding was not corroborated in other studies, which, however, looked at smaller study populations. We did not identify a meaningful difference in our meta-analysis, which was based on two trials including the aforementioned one (relative risk 1.36, 95% CI 0.55–3.38, I^2=85%, 276 participants, very low certainty) [31, 40].

Cough as an outcome was captured mostly using nonvalidated scores in eight trials, six of which demonstrated potential benefit with mucolytics. A higher proportion of participants receiving mucolytics experienced post-treatment absence of cough compared to the control group (relative risk 1.93, 95% CI 1.15–3.23, I^2= 29%, 276 participants, moderate certainty) [31, 40]. In addition, post-treatment ease of expectoration improved significantly with mucolytics *versus* control (relative risk 2.94, 95% CI 1.68–5.12, I^2=0%, 149 participants, moderate certainty). Sputum viscosity was assessed using nonvalidated scores in four trials, three of which showed significant improvement for the mucolytic group.

Health-related quality of life was addressed using the mean change from pre-treatment score in the clinical COPD questionnaire in one study with 78 participants [39], which suggested the superiority of mucolytics

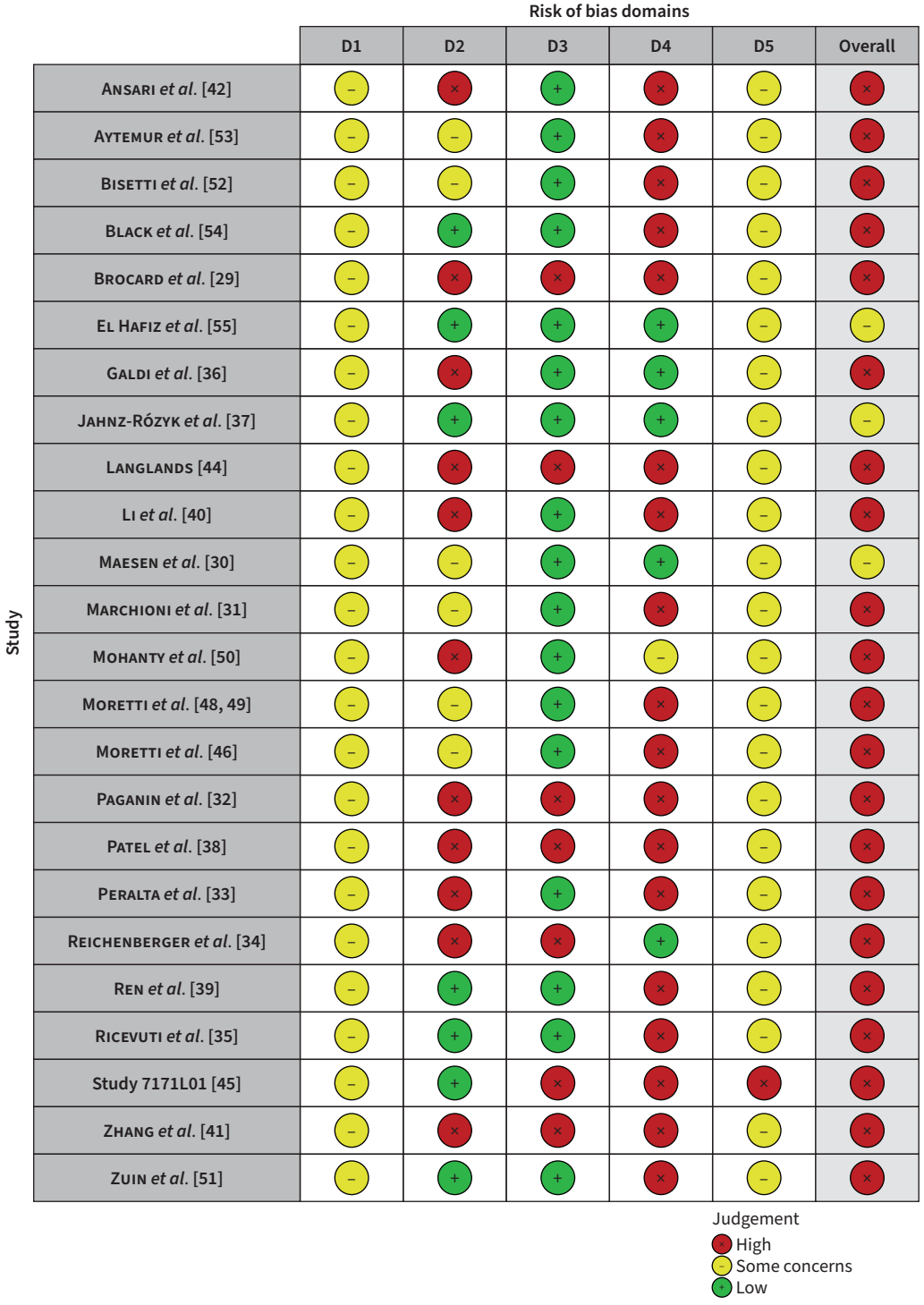


FIGURE 1 Risk of bias table. D1: bias arising from the randomization process; D2: bias due to deviations from the intended intervention; D3: bias due to missing outcome data; D4: bias in measurement of the outcome; D5: bias in selection of the reported result.

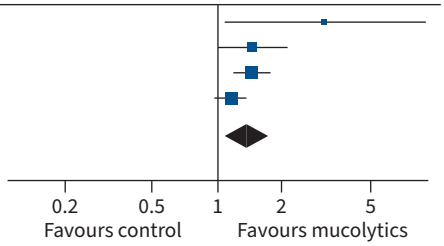
compared to control, although between-group difference did not exceed the minimal clinically important difference (MD 0.7, 95% CI 0.6–0.8, low certainty).

Mucolytics were not found to reduce length of hospital stay in five of the six trials that reported this outcome, with median lengths ranging from 6 to 10.5 days in the intervention and from 5.5 to 10.2 days in

a)

Study or subgroup	Mucolytics Events	Total	Placebo or standard Events	Total	Weight (%)	Risk ratio M–H, random, 95% CI
Bisetti *et al.* [52]	10	14	3	13	4.6	3.10 (1.09–8.81)
Li *et al.* [40]	20	24	15	26	21.4	1.44 (0.99–2.10)
Marchioni *et al.* [31]	91	114	62	112	35.7	1.44 (1.19–1.74)
Zhang *et al.* [41]	38	40	33	40	38.3	1.15 (0.98–1.35)
Total (95% CI)		**192**		**191**	**100.0**	**1.37 (1.08–1.73)**
Total events	159		113			

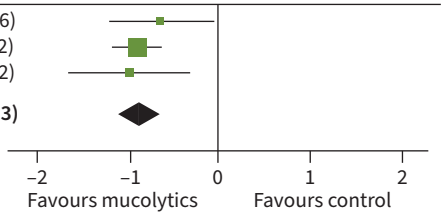
Heterogeneity: Tau²=0.03; Chi²=8.20, df=3 (p=0.04); I²=63%
Test for overall effect: z=2.62 (p=0.009)



b)

Study or subgroup	Mucolytics Mean	SD	Total	Placebo or standard Mean	SD	Total	Weight (%)	SMD IV, random, 95% CI
Li *et al.* [40]	3.3	2.3	24	6.1	5.6	26	16.4	−0.63 (−1.20 to −0.06)
Marchioni *et al.* [31]	4.92	2.66	114	1.38	2.83	112	71.3	−0.89 (−1.17 to−0.62)
Moretti *et al.* [46]	4.4	0.9	20	5.4	1.1	20	12.3	−0.98 (−1.63 to −0.32)
Total (95% CI)		**158**			**158**		**100.0**	**−0.86 (−1.09 to −0.63)**

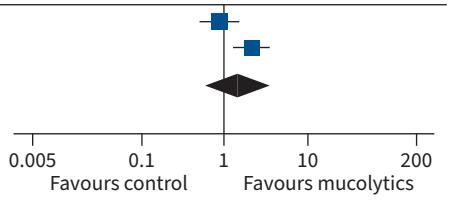
Heterogeneity: Tau²=0.00; Chi²=0.78, df=2 (p=0.68); I²=0%
Test for overall effect: z=7.30 (p<0.00001)



c)

Study or subgroup	Mucolytics Events	Total	Placebo or standard Events	Total	Weight (%)	Risk ratio M–H, random, 95% CI
Li *et al.* [40]	12	24	15	26	49.4	0.87 (0.52–1.45)
Marchioni *et al.* [31]	41	114	19	112	50.6	2.12 (1.32–3.42)
Total (95% CI)		**138**		**138**	**100.0**	**1.36 (0.55–3.38)**
Total events	53		34			

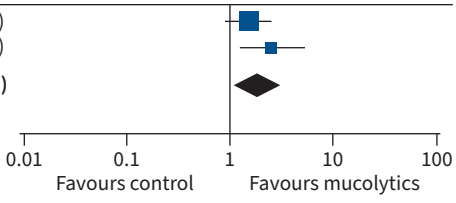
Heterogeneity: Tau²=0.36; Chi²=6.63, df=1 (p=0.01); I²=85%
Test for overall effect: z=0.67 (p=0.50)



d)

Study or subgroup	Mucolytics Events	Total	Placebo or standard Events	Total	Weight (%)	Risk ratio M–H, random, 95% CI
Li *et al.* [40]	16	24	11	26	60.6	1.58 (0.93–2.68)
Marchioni *et al.* [31]	24	114	9	112	39.4	2.62 (1.27–5.38)
Total (95% CI)		**138**		**138**	**100.0**	**1.98 (1.15–3.23)**
Total events	40		20			

Heterogeneity: Tau²=0.04; Chi²=1.41, df=1 (p=0.24); I²=29%
Test for overall effect: z=2.48 (p=0.01)



e)

Study or subgroup	Mucolytics Events	Total	Placebo or standard Events	Total	Weight (%)	Risk ratio M–H, random, 95% CI
Langlands [44]	9	13	4	14	37.8	2.42 (0.98–5.98)
Zuin *et al.* [51]	44	80	7	42	62.2	3.30 (1.63–6.68)
Total (95% CI)		**93**		**56**	**100.0**	**2.94 (1.68–5.12)**
Total events	53		11			

Heterogeneity: Tau²=0.00; Chi²=0.29, df=1 (p=0.59); I²=0%
Test for overall effect: z=3.80 (p=0.0001)

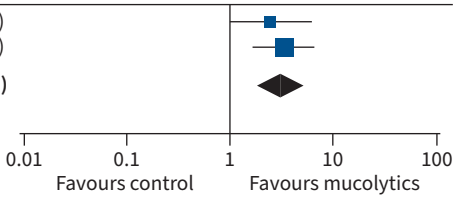


FIGURE 2 Forest plots depicting the overall effect estimates for the following outcomes upon treatment completion: a) treatment success; b) overall symptom scores; c) absence of breathlessness; d) absence of cough; e) ease of expectoration. M–H: Mantel–Haenszel method; SMD: standardised mean difference.

the control groups. Three trials reported adequate data for inclusion in a meta-analysis, which did not reveal between-group differences (MD −1.04, 95% CI −4.66–2.58, I^2=76%, 114 participants, low certainty). Indication for a higher level of care was noted in two studies as admission to the ICU and intubation [36, 53] with no significant difference between groups (relative risk 0.36, 95% CI 0.06–2.17, I^2=0%, 83 participants, low certainty).

https://doi.org/10.1183/16000617.0141-2022

TABLE 2 Grading of Recommendation, Assessment, Development and Evaluation (GRADE) evidence profile

Outcome	Measure	n (N)	Effect estimates	Certainty						Benefit
				Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Overall certainty	
Treatment success	N	4 (383)	Relative risk 1.37 (1.08–1.73), I^2=63%	Serious[#]	Not serious	Not serious	Not serious	Not serious	Moderate	Yes
Overall symptom score	Post-treatment scores	3 (316)	SMD 0.86 (0.63–1.09), I^2=0%	Serious[#]	Not serious	Not serious	Not serious	Not serious	Moderate	Yes
	Change from pre-treatment	1 (50)	SMD 0.80 (0.22–1.38)	Serious[#]	Not serious	Not serious	Not serious	Not serious		
	N with improvement	1 (200)	Relative risk 1.18 (1.07–1.31)	Serious[#]	Not serious	Not serious	Not serious	Not serious		
	Dyspnoea cough attacks	1 (30)	MD −1.40 (−3.51–0.71)	Serious[#]	Not serious	Not serious	Serious[¶]	Not serious		
Breathlessness	N with absence	2 (276)	Relative risk 1.36 (0.55–3.38), I^2=85%	Serious[#]	Serious[+]	Not serious	Serious[¶]	Not serious	Very low	No
	Change from pre-treatment in Borg's scale	1 (59)	MD 0.40 (−0.55–1.35)	Serious[#]	Not serious	Not serious	Serious[¶]	Not serious		
	N with improvement	1 (27)	Relative risk 1.08 (0.69–1.68)	Serious[#]	Not serious	Not serious	Serious[¶]	Not serious		
	N with dyspnoea at rest	1 (40)	Relative risk 0.18 (0.01–3.56)	Serious[#]	Not serious	Not serious	Serious[¶]	Not serious		
Cough	N with absence	2 (276)	Relative risk 1.93 (1.15–3.23), I^2=29%	Serious[#]	Not serious	Not serious	Not serious	Not serious	Moderate	Yes
	N with improvement in frequency/in intensity	1 (122)	Relative risk 1.40 (0.88–2.22)/ Relative risk 2.06 (1.23–3.43)	Serious[#]	Not serious	Not serious	Serious[¶]	Not serious		
Ease of expectoration	N with improvement	2 (149)	Relative risk 2.94 (1.68–5.12), I^2=0%	Serious[#]	Not serious	Not serious	Not serious	Not serious	Moderate	Yes
	N with absence	1 (226)	Relative risk 3.71 (1.87–7.38)	Serious[#]	Not serious	Not serious	Not serious	Not serious		
Health-related quality of life	Change from pre-treatment	1 (78)	MD 0.7 (0.6–0.8)	Serious[#]	Not serious	Not serious	Serious[¶]	Not serious	Low	Yes
Length of hospital stay	Mean duration in days	3 (114)	MD −1.04 (−4.66–2.58), I^2=76%	Serious[#]	Not serious	Not serious	Serious[¶]	Not serious	Low	No
ICU admission and ventilation	N	2 (83)	Relative risk 0.36 (0.06–2.17), I^2=0%	Serious[#]	Not serious	Not serious	Serious[¶]	Not serious	Low	No
Future exacerbations	N with re-exacerbation at day 30	2 (55)	Relative risk 0.08 (0.00–1.28)	Serious[#]	Not serious	Not serious	Serious[¶]	Not serious	Very Low	Yes
	HR, 2 months follow-up	1 (40)	HR 0.169 (0.033–0.875)	Serious[#]	Not serious	Not serious	Serious[¶]	Not serious		
	Time to first (days), 6 months follow-up	1 (38)	MD 27.70 (−4.55–59.95)	Serious[#]	Not serious	Not serious	Serious[¶]	Not serious		
Mortality	N	4 (173)	Relative risk 0.73 (0.11–4.90), I^2=16%	Serious[#]	Not serious	Not serious	Serious[¶]	Not serious	Low	No
SAEs	N	2 (109)	No SAEs were observed	Serious[#]	Not serious	Not serious	Serious[¶]	Not serious	Low	No risk

[#]All studies included in this systematic review were deemed to be of at least some concern of methodological bias. [¶]Broad confidence intervals and/or insufficient overall study population. [+]Marchioni *et al.* [31] reported significant improvement in dyspnoea; however, significance was lost in a meta-analysis that included a second, smaller randomised controlled trial. n: Number of trials; N: number of patients; HR: hazard ratio; ICU: intensive care unit; MD: mean difference; SAE: serious adverse event; SMD: standardised mean difference.

https://doi.org/10.1183/16000617.0141-2022

TABLE 3 Summary of evidence per mucolytic, per outcome

Mucolytics/outcomes	N-Acetylcysteine	Ambroxol	Erdosteine	Bromhexine	Hypertonic saline	Hyaluronan
Treatment success	NA	N=50 (+) N with resolution or significant improvement of symptoms and laboratory findings [40] N=80 (+) N with clinical efficacy [41]	N=27 (+) N with clinical judgement of effectiveness [52] N=226 (+) N with resolution of symptoms [31]	NA	NA	NA
Patient reported	NA	30 (–) Number of dyspnoea and cough attacks [37]	226 (+) Global clinical assessment score [31] 200 (+) N with improvement [50]	NA	NA	NA
Overall symptom score	NA	50 (+) Chinese medical symptom score, mean change [40]	55 (+) Breathlessness–sputum–cough scale [46, 48]	NA	NA	
Breathlessness	40 (–) N per severity [42] 88 (–) Likert score 0–7, nonvalidated [53, 54]	50 (–) Chinese medical symptom score [40]	226 (+) Nonvalidated score 0–3 [31] N with absence [31]	27 (–) N with improvement [44]	59 (–) Modified Borg scale [38]	NA
Cough	38 (–) Nonvalidated score 0–7 [53] 95 (+) Nonvalidated score 0–3 [29] 122 (+) N with improvement in intensity [51]	50 (+) N with severe cough affecting sleep, Chinese medical symptom score [40] 23 (–) Nonvalidated score 0–3 [33]	253 (+) Nonvalidated score 0–3 [31, 52] 226 (+) N with absence [31] (same study as above)	NA	NA	NA
Ease of expectoration	38 (–) Nonvalidated score 0–7 [53] 122 (+) N with improvement [51]	50 (–) Chinese medical symptom score [40] 23 (+) Nonvalidated score 0–3 [33]	253 (+) Nonvalidated score 0–3 [31, 52] 226 (+) N with absence [31] (same study as above)	27 (–) N with improvement [44]	NA	NA
Sputum viscosity	30 (+) Nonvalidated score 0–3 [35]	NA	27 (+) Centipoises, mean % change, compared to pre-treatment [52] 226 (+) Nonvalidated score 0–3 [31] N with fluid saliva [31]	27 (–) Centipoises and arbitrary units [44]	NA	NA
Health-related quality of life	78 (+) Clinical COPD questionnaire, mean change [39]					
Hospitalisation duration	166 (–) [39, 53, 54]	NA	52 (–) [46, 47]	NA	NA	36 (+) [36]
Indication for higher level of care	42 (–) N with ICU admission and intubation [53]	NA	NA	NA	NA	41 (–) N needing invasive ventilation [36]
Future exacerbations	38 (–) Rate by 6 months [53] Time to first by 6 months [53]	NA	40 (+) N by day 30 [46] Hazard ratio by day 60 [46] 15 (–) Rate by day 30 [49] (+) Rate by day 60 [49]	NA	NA	NA
Mortality	42 (–) N [53]	NA	NA	31 (–) N [44]	59 (–) N up to 30 days [43]	41 (–) N [36]
Serious adverse events	50 (–) None [54]	NA	NA	NA	59 (–) None [43]	NA

Various measurement instruments were used for assessing some of the outcomes. Results are pooled per instrument and for each instrument we present the overall population in which it was tested and whether there was evidence (+) or no evidence (–) of a beneficial effect with mucolytics. ICU: intensive care unit; N: number of participants; NA: not assessed in any trial.

Future exacerbations were captured in three trials. Two small studies assessed patients with re-exacerbation at 30 days and they did not reveal between-group differences (relative risk 0.08, 95% CI 0.0–1.3). Two studies assessed time-to-next exacerbation. One concluded that mucolytics delay the next exacerbation (hazard ratio 0.169, 95% CI 0.03–0.88, 40 participants, 2 months follow-up) [46], with the second showing a similar trend (MD 27.70 days, 95% CI −4.55–59.95, 38 participants, 6 months follow-up) [53]. The latter also suggested that mucolytics may delay the next hospitalisation (MD 21 days, 95% CI −14.5–56.5), but future hospitalisation rate was not affected (MD 0.30, 95% CI −0.34–0.94, 38 participants), as confirmed by a second study [38] (relative risk 1.03, 95% CI 0.23–4.71, 59 participants). Overall, mucolytics may delay future exacerbations and hospitalisation (very low certainty).

Safety data were only scarcely reported across the included studies. Mortality was reported in four trials, which did not reveal between-group differences (relative risk 0.73, 95% CI 0.11–4.90, I^2=16%, 173 participants, very low certainty). Serious adverse events were monitored in two trials (109 participants); they did not capture any events in either treatment arm, supporting the safety of mucolytics (low certainty). Four studies reported data on adverse events that we were able to analyse. They did not reveal between-group differences (relative risk 0.74, 95% CI 0.23–2.32, I^2=0%, 272 participants, very low certainty), while other trials narratively reported balanced side effects across the study groups.

Arterial blood gas parameters were evaluated in seven studies. We were able to analyse data on the partial pressure of oxygen in arterial blood (P_{aO_2} in mmHg) from four trials [39, 42, 53, 55] that revealed a slightly higher P_{aO_2} in the mucolytics group (MD 3.21, 95% CI 1.51–4.92 mmHg, I^2=38%, 201 participants). We found similar results for oxygen saturation (S_{aO_2} in %, MD 0.96, 95% CI 0.27–1.66, I^2=0%, 123 participants). On the other hand, mucolytics did not appear to have any impact on the partial pressure of carbon dioxide (P_{aCO_2} in mmHg, MD −1.09, 95% CI −2.40–0.23, I^2=37%, 201 participants).

The ERS COPD exacerbations core outcome set recommended assessing the impact of exacerbations on disease progression as a change in forced expiratory volume in 1 s (FEV_1) from baseline [24]. While none of the included trials assessed this outcome, 13 reported on lung function after exacerbation. Post-treatment FEV_1 did not differ between treatment arms, both when assessing percentage of the predicted values (MD 2.74, 95% CI −1.24–6.72, I^2=81%, four studies, 193 participants) and absolute values in millilitres (MD 120.29, 95% CI −103.45–344.03, I^2=81%, 156 participants). Five out of eight trials that did not report adequate data for inclusion in our meta-analysis did not suggest between-group differences either. While we were not able to pool data for forced vital capacity due to poor reporting, most trials suggested a limited treatment effect on this parameter.

A microbiological outcome was assessed in five trials. Out of 74 patients with a positive sputum culture on admission, 45 achieved a negative post-treatment result, with similar proportions across treatment groups (relative risk 1.65, 95% CI 0.69–3.98, I^2=68%).

Activities of daily living, worsening of symptoms after initial treatment, development of pneumonia and treatment adherence were not reported in any of the included studies.

Subgroup and sensitivity analyses

All planned subgroup analyses are presented in the online appendix. Moreover, table 3 summarises our findings for each mucolytic agent. While our subgroup analyses revealed some potential between-group differences, these analyses were based on very small study populations per subgroup, thus significantly limiting our confidence in the findings.

No study had a low risk of bias and it was therefore not feasible to perform any of the pre-specified sensitivity analyses. The fixed-effect model sensitivity analysis suggested a positive treatment impact of mucolytics on some additional outcomes, such as 1) post-treatment absence of breathlessness, 2) post-treatment P_{aCO_2}, 3) post-treatment FEV_1 and 4) pathogen clearance in sputum culture. However, in view of the clinical and methodological heterogeneity identified, we believe our main analysis is more appropriate.

Discussion

This systematic review and meta-analysis, based on 24 RCTs looking at 2192 patients with a moderate or severe COPD exacerbation, demonstrated with moderate certainty that mucolytics increase the rate of treatment success by 37% and are associated with a clinically meaningful improvement in symptoms. Mucolytics also appear to reduce cough and ease sputum expectoration (moderate certainty). In addition, low or very low certainty evidence suggests that mucolytics may also reduce the risk of future

exacerbations and improve health-related quality of life, but do not seem to have an impact on breathlessness, length of hospital stay, indication for higher level of care or serious adverse events. It should be highlighted that due to heterogeneity in the outcomes and the outcome measurement instruments used, as well as inadequate reporting of relevant outcome data by some trials, each of the meta-analyses presented in this report were informed by data from up to four trials.

Airway mucus hypersecretion presents a key treatable trait in COPD. In stable disease state, it is associated with lung function decline, impaired quality of life, risk of hospitalisation and mortality [57, 58]. During exacerbations, airway mucus hypersecretion aggravates expectoration difficulty, airway inflammation and obstruction, as well as bacterial adhesiveness, thus creating a vicious cycle [18, 59, 60]. By regulating the viscoelastic properties of mucus and facilitating sputum expectoration, mucolytics may resolve this vicious cycle, thus improving the outcomes of exacerbations.

Head-to-head comparisons of different mucolytics are only evaluated in a few small trials that do not allow us to draw confident conclusions [61–64]. Interestingly, in a double-blinded trial involving 426 patients with COPD exacerbation, Prabhu Shankar *at al.* [65] demonstrated the superiority of the combination of bromhexine and guaiphenesin, compared to the monocomponents, suggesting a potential role for combining mucolytics with different mechanisms of action.

Mucolytics for the management of stable COPD have been evaluated in 38 trials totalling 10 377 participants, which were synthesised in a Cochrane review by Poole *et al.* [19]. Firstly, consistent with our findings, their review did not reveal any meaningful difference in adverse events. Furthermore, moderate-certainty evidence suggested that maintenance treatment with mucolytics confers a modest benefit in preventing exacerbations, reducing the days of disability per month and, possibly, the rate of hospitalisation. Similar to our work, this meta-analysis was limited by the fact that most included RCTs did not specifically recruit patients suffering from the airway secretion of highly viscous or voluminous mucus. Therefore, these findings are also possibly weakened by the limited effect in patients lacking this trait.

A limitation of our work is that we were not able to access the full text of six older, potentially eligible studies. However, we were able to capture the main study characteristics and outcomes of three of these RCTs from their abstracts and we included them in our meta-analysis [34, 41, 50]. Overall, with 24 RCTs including almost 2200 patients with moderate or severe COPD exacerbations, this is a broad systematic review, aggregating the best currently available evidence, which could be used to drive clinical practice and future research. Indeed, previous systematic reviews considered up to 15 of the included studies [66, 67, 68]. In addition, we followed the rigorous methodologies recommended by Cochrane and the GRADE working group for synthesising the available evidence and assessing methodological quality at the level of the included studies and of the overall body of evidence.

Another potential limitation of our study is that we did not include any real-life evidence. However, considering the heterogeneity of COPD exacerbations and the established practice to administer mucolytics only to patients with expectoration difficulty or thick sputum, this data would be at a high risk of indication bias.

It has been postulated that mucolytics are particularly effective in patients with exacerbations characterised by hypersecretion of thick sputum that is difficult to expectorate. However, mucolytics have also been attributed other beneficial effects besides liquifying sputum, such as antioxidant or immunomodulatory effects [17]. Our meta-analysis was based on studies evaluating unselected patients with moderate or severe exacerbations; stronger effects might be anticipated among patients presenting with increased sputum volume and viscosity. We did not have adequate data to assess the impact of mucolytics on this group of patients. In fact, all our subgroup analyses were limited by the very small study populations per subgroup.

Our certainty of the overall evidence was moderate for the primary outcomes and moderate to very low for the remaining outcomes. Significant methodological limitations inherent to most of the included studies and considerable heterogeneity in the reported outcomes and outcome measurement instruments limited our availability to pool data from the different studies. In our review, we evaluated all critically important outcomes that have been prioritised in the recently published ERS COPD exacerbations core outcome set [24]. We note, however, that only a handful of these outcomes have been consistently adopted in the completed RCTs, with some studies not reporting on any at all. We would encourage the adoption of this core outcome set in future trials, with a view to increasing consistency in the selection of outcomes that matter most to patients and clinicians.

National and international clinical practice guidelines do not currently recommend mucolytics for the management of COPD exacerbations [69–72]. As a result, their uptake varies significantly between different countries, health systems and even clinicians working in the same department. As a result, observational studies report administration of mucolytics in 2.0–72.5% of all exacerbations [73, 74]. Our findings suggest that mucolytics should be considered for these patients.

Well-designed and adequately powered trials are warranted to further assess the impact of mucolytics on all COPD exacerbation outcomes that are critically important to patients and other stakeholders. Importantly, such trials will need to assess the effects of mucolytics in patients with exacerbations characterised by increased sputum volume or thickness. The MucAct is an important ongoing double-blind randomised controlled trial in the UK (EudraCT number: 2020–001949–39) that fulfils these characteristics and intends to assess hypertonic saline *versus* placebo in 860 patients with this trait. In addition, in view of the significant heterogeneity of COPD exacerbations that necessitates the introduction of precision medicine interventions, the DECODE-NET (DisEntangling Chronic Obstructive pulmonary Disease Exacerbations – an international clinical trials NETwork) aspires to launch a platform trial that will evaluate precision medicine interventions to address various treatable traits of COPD exacerbations [75].

In conclusion, our meta-analysis synthesised the best available evidence on the safety and clinical effectiveness of mucolytics for COPD exacerbations and concluded with moderate certainty that mucolytics appear to improve the treatment success rate and symptoms. Therefore, mucolytics could be considered for the management of patients with COPD exacerbations. Our work also revealed significant limitations of the available research evidence that warrant addressing in future adequately powered and well-conducted RCTs.

Questions for future research

Large and well-conducted RCTs are needed to further assess the clinical effectiveness of various mucolytics for unselected patients with COPD exacerbations, as well as those associated with hypersecretion of thick mucus. As a minimum, they should address the outcomes most important to patients and other stakeholders that are included in the ERS COPD exacerbations core outcome set.

Provenance: Submitted article, peer reviewed.

Author contributions: Study conception: E. Papadopoulou, J. Vestbo, A.G. Mathioudakis. Study design: E. Papadopoulou, A.G. Mathioudakis. Methodological expertise: A.G. Mathioudakis. Screening, study selection, data extraction, risk of bias assessment: E. Papadopoulou, J. Hansel, A.G. Mathioudakis. Meta-analysis: E. Papadopoulou, A.G. Mathioudakis. Manuscript drafting: E. Papadopoulou, A.G. Mathioudakis. Interpretation of findings: All authors. Critical revision of the manuscript: All authors.

Support statement: E. Papadopoulou was supported by the Greek-British Cooperation on Short-Term Scholarships (2022-0311-20124). J. Vestbo and A.G. Mathioudakis were supported by the National Institute for Health and Care Research Manchester Biomedical Research Centre (NIHR Manchester BRC). A.G. Mathioudakis was supported by an NIHR Clinical Lectureship in Respiratory Medicine. J. Hansel was supported by an NIHR Academic Clinical Fellowship in Intensive Care Medicine.

Conflicts of interest: The authors declare no conflict of interest related to this work. E. Papadopoulou, J. Hansel, and Z. Lazar report no conflict of interest. K. Kostikas reports grants from AstraZeneca, Boehringer Ingelheim, Chiesi, Innovis, ELPEN, GSK, Menarini, Novartis and NuvoAir, consulting fees from AstraZeneca, Boehringer Ingelheim, Chiesi, CSL Behring, ELPEN, GSK, Menarini, Novartis and Sanofi Genzyme, honoraria from AstraZeneca, Boehringer Ingelheim, Chiesi, ELPEN, GILEAD, GSK, Menarini, MSD, Novartis, Sanofi Genzyme and WebMD. S. Tryfon reports honoraria from Menarini, Boehringer-Ingelheim and ELPEN, support for attending meetings from Chiesi and Menarini, and patents with GSK, AstraZeneca and ELPEN, not related to this work. J. Vestbo reports consulting fees and/or honoraria from ALK-Abello, AstraZeneca, Boehringer Ingelheim, GSK and TEVA, not related to this work. A.G. Mathioudakis reports a research grant from Boehringer Ingelheim, not related to this work.

References

1 BD 2017 DALYs and HALE Collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018; 392: 1859–1922.

2 World Health Organization. Chronic obstructive pulmonary disease (COPD). www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-(copd) Date last accessed: 27 May 2022. Date last updated: 20 May 2022.
3 Seemungal TA, Hurst JR, Wedzicha JA. Exacerbation rate, health status and mortality in COPD--a review of potential interventions. *Int J Chron Obstruct Pulmon Dis* 2009; 4: 203–223.
4 Donaldson GC, Wedzicha JA. COPD exacerbations. 1: Epidemiology. *Thorax* 2006; 61: 164–168.
5 Donaldson GC, Law M, Kowlessar B, *et al.* Impact of prolonged exacerbation recovery in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2015; 192: 943–950.
6 Mathioudakis AG, Vanfleteren LEGW, Lahousse L, *et al.* Current developments and future directions in COPD. *Eur Respir Rev* 2020; 29: 200289.
7 Global Initiative for Chronic Obstructive Lung Disease (GOLD). 2022 GOLD Reports. https://goldcopd.org/2022-gold-reports-2/ Date last accessed: 10 May 2022.
8 Agustí A, Bafadhel M, Beasley R, *et al.* Precision medicine in airway diseases: moving to clinical practice. *Eur Respir J* 2017; 50: 1701655.
9 Agusti A, Bel E, Thomas M, *et al.* Treatable traits: toward precision medicine of chronic airway diseases. *Eur Respir J* 2016; 47: 410–419.
10 McDonald VM, Fingleton J, Agusti A, *et al.* Treatable traits: a new paradigm for 21st century management of chronic airway diseases: Treatable Traits Down Under International Workshop report. *Eur Respir J* 2019; 53: 1802058.
11 Rochwerg B, Brochard L, Elliott MW, *et al.* Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. *Eur Respir J* 2017; 50: 1602426.
12 Mathioudakis AG, Janssens W, Sivapalan P, *et al.* Acute exacerbations of chronic obstructive pulmonary disease: in search of diagnostic biomarkers and treatable traits. *Thorax* 2020; 75: 520–527.
13 Mathioudakis AG, Chatzimavridou-Grigoriadou V, Corlateanu A, *et al.* Procalcitonin to guide antibiotic administration in COPD exacerbations: a meta-analysis. *Eur Respir Rev* 2017; 26: 160073.
14 Sivapalan P, Lapperre TS, Janner J, *et al.* Eosinophil-guided corticosteroid therapy in patients admitted to hospital with COPD exacerbation (CORTICO-COP): a multicentre, randomised, controlled, open-label, non-inferiority trial. *Lancet Respir Med* 2019; 7: 699–709.
15 Curran DR, Cohn L. Advances in mucous cell metaplasia: a plug for mucus as a therapeutic focus in chronic airway disease. *Am J Respir Cell Mol Biol* 2010; 42: 268–275.
16 Williams OW, Sharafkhaneh A, Kim V, *et al.* Airway mucus: from production to secretion. *Am J Respir Cell Mol Biol* 2006; 34: 527–536.
17 Balsamo R, Lanata L, Egan CG. Mucoactive drugs. *Eur Respir Rev* 2010; 19: 127–133.
18 Rogers DF. The role of airway secretions in COPD: pathophysiology, epidemiology and pharmacotherapeutic options. *COPD* 2005; 2: 341–353.
19 Poole P, Sathananthan K, Fortescue R. Mucolytic agents versus placebo for chronic bronchitis or chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* 2019; 5: CD001287.
20 Papadopoulou E, Tryfon S, Kostikas K, *et al.* Mucolytics as add-on treatment for acute exacerbations of chronic obstructive pulmonary disease. *PROSPERO* 2022: CRD42022314958. www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022314958
21 Higgins JPT, Thomas J, Chandler J, *et al.* eds. Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022). Cochrane, 2022. www.training.cochrane.org/handbook
22 Guyatt GH, Oxman AD, Vist GE, *et al.* GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008; 336: 924–926.
23 Page MJ, McKenzie JE, Bossuyt PM, *et al.* The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021; 372: n71.
24 Mathioudakis AG, Abroug F, Agusti A, *et al.* ERS statement: a core outcome set for clinical trials evaluating the management of COPD exacerbations. *Eur Respir J* 2022; 59: 2102006.
25 Mathioudakis AG, Ananth S, Bradbury T, *et al.* Assessing treatment success or failure as an outcome in randomised clinical trials of COPD exacerbations. A Meta-Epidemiological Study. *Biomedicines* 2021; 9: 1837.
26 Sterne JAC, Savović J, Page MJ, *et al.* RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019; 366: l4898.
27 McGuinness LA, Higgins JPT. Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments. *Res Synth Methods* 2021; 12: 55–61.
28 Balshem H, Helfand M, Schünemann HJ, *et al.* GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol* 2011; 64: 401–406.
29 Brocard H, Charpin J, Germouty J. Multicenter, doubleblind study of oral acetylcysteine vs. placebo. *Eur J Respir Dis Suppl* 1980; 111: 65–69.
30 Maesen FP, Davies BI, Brouwers J, *et al.* Erythromycin and bromhexine in acute exacerbations of chronic bronchitis. A study on sputum penetration and clinical effectiveness. *Eur J Respir Dis* 1982; 63: 325–329.

31 Marchioni CF, Polu JM, Taytard A, *et al.* Evaluation of efficacy and safety of erdosteine in patients affected by chronic bronchitis during an infective exacerbation phase and receiving amoxycillin as basic treatment (ECOBES, European Chronic Obstructive Bronchitis Erdosteine Study). *Int J Clin Pharmacol Ther* 1995; 33: 612–618.

32 Paganin F, Bouvet O, Chanez P, *et al.* Evaluation of the effects of ambroxol on the ofloxacin concentrations in bronchial tissues in COPD patients with infectious exacerbation. *Biopharm Drug Dispos* 1995; 16: 393–401.

33 Peralta J, Poderoso JJ, Corazza C, *et al.* Ambroxol plus amoxicillin in the treatment of exacerbations of chronic bronchitis. *Arzneimittelforschung* 1987; 37: 969–971.

34 Reichenberger F, Tamm M. Nacetylcystein in the therapy of chronic bronchitis. *Pneumologie* 2002; 56: 793–797.

35 Ricevuti G, Pasotti D, Mazzone A, *et al.* Serum, sputum and bronchial concentrations of erythromycin in chronic bronchitis after single and multiple treatments with either propionate-N-acetylcysteinate or stearate erythromycin. *Chemotherapy* 1988; 34: 374–379.

36 Galdi F, Pedone C, McGee CA, *et al.* Inhaled high molecular weight hyaluronan ameliorates respiratory failure in acute COPD exacerbation: a pilot study. *Respir Res* 2021; 22: 30.

37 Jahnz-Rózyk K, Kucharczyk A, Chciałowski A, *et al.* Wpływ leczenia wziewna postacia ambroksolu na objawy kliniczne i wybrane parametry wentylacji u chorych hospitalizowanych z powodu zaostrzenia przewlekłej obturacyjnej choroby płuc [The effect of inhaled ambroxol treatment on clinical symptoms and chosen parameters of ventilation in patients with exacerbation of chronic obstructive pulmonary disease patients]. *Pol Merkur Lekarski* 2001; 11: 239–243.

38 Patel K, McNeilly R, Collins C, *et al.* Nebulized hypertonic saline for inpatient use in COPD. *Chest* 2017; 152 Suppl. 4, A786.

39 Ren F, Jiang Y. Application of N-acetylcysteine inhalation in treatment of elderly patients with acute exacerbation of chronic obstructive pulmonary disease. *J Jilin Univ Med Ed* 2019; 45: 1141–1145.

40 Li W, Mao B, Wang G, *et al.* Effect of tanreqing injection on treatment of acute exacerbation of chronic obstructive pulmonary disease with Chinese medicine syndrome of retention of phlegm and heat in Fei. *Chin J Integr Med* 2010; 16: 131–137.

41 Zhang Q, He Z, Tan MQ. Efficacy of ambroxol hydrochloride intravenous injection adjunctive treatment for acute exacerbation of chronic obstructive pulmonary disease. *Pract Pharm Clin Remedies* 2013; 16: 337–338.

42 Ansari SF, Memon M, Brohi N, *et al.* N-acetylcysteine in the management of acute exacerbation of chronic obstructive pulmonary disease. *Cureus* 2019; 11: e6073.

43 ClinicalTrials.gov. Nebulized hypertonic saline for inpatient use in COPD. ClinicalTrials.gov identifier: NCT02266875. https://clinicaltrials.gov/ct2/show/results/NCT02266875 Date last updated: 22 November 2017. Date last accessed: 4 July 2022.

44 Langlands JH. Double-blind clinical trial of bromhexine as a mucolytic drug in chronic bronchitis. *Lancet* 1970; 1: 448–450.

45 Clinical Trial Report Synopsis Study 7171L01. A randomized, double-blind, placebo controlled, parallel groups study on efficacy and safety of NAC 600 mg daily and NAC 1200 mg daily as mucolytic agent in the treatment of chronic obstructive pulmonary disease (COPD) exacerbation. www.clinicaltrialsregister.eu/ctr-search/trial/2006-004048-21/results Date last updated: 23 April 2016.

46 Moretti M, Fagnani S. Erdosteine reduces inflammation and time to first exacerbation postdischarge in hospitalized patients with AECOPD. *Int J Chron Obstruct Pulmon Dis* 2015; 10: 2319–2325.

47 Bianchi B, Ballabio M, Moretti M. Effects of erdosteine on serum biomarker concentrations at COPD exacerbation. *Eur Respir J* 2010; 36: Suppl. 54, 378.

48 Moretti M, Ballabio M. Effect of erdosteine on airflow obstruction and symptom recovery in severe COPD exacerbations. *Eur Respir J* 2011; 38: Suppl. 55, 536.

49 Moretti M, Ballabio M. Acute effect of erdosteine on preventing recurrence of exacerbation in COPD patients after hospital discharge. *Eur Respir J* 2012; 40: Suppl. 56, 2881.

50 Mohanty KC, Thiappanna G, Singh V, *et al.* Evaluation of efficacy and safety of erdosteine in patients affected by exacerbation of chronic bronchitis and receiving ciprofloxacin as basic treatment. *J Clin Res* 2001; 4: 35–39.

51 Zuin R, Palamidese A, Negrin R, *et al.* High-dose N-acetylcysteine in patients with exacerbations of chronic obstructive pulmonary disease. *Clin Drug Investig* 2005; 25: 401–408.

52 Bisetti A, Mancini C. Mucolytic activity of erdosteine: Double blind clinical trial vs. placebo. *Arch Medicina Interna* 1995; 47: 89–97.

53 Aytemur ZA, Baysak A, Ozdemir O, *et al.* N-acetylcysteine in patients with COPD exacerbations associated with increased sputum. *Wien Klin Wochenschr* 2015; 127: 256–261.

54 Black PN, Morgan-Day A, McMillan TE, *et al.* Randomised, controlled trial of N-acetylcysteine for treatment of acute exacerbations of chronic obstructive pulmonary disease [ISRCTN21676344]. *BMC Pulm Med* 2004; 4: 13.

55 El Hafiz AMA, El Wakeel LM, El Hady HM, *et al.* High dose N-acetyl cysteine improves inflammatory response and outcome in patients with COPD exacerbations. *Egypt J Chest Dis Tuberc* 2013; 62: 51–57.

56 Moretti M. Erdosteine improves airflow in patients with severe exacerbation of COPD (AECOPD). *Eur Respir J* 2016; 48: Suppl. 60, A4077.

57 Vestbo J, Prescott E, Lange P. Association of chronic mucus hypersecretion with FEV_1 decline and chronic obstructive pulmonary disease morbidity. Copenhagen City Heart Study Group. *Am J Respir Crit Care Med* 1996; 153: 1530–1535.

58 Ramos FL, Krahnke JS, Kim V. Clinical issues of mucus accumulation in COPD. *Int J Chron Obstruct Pulmon Dis* 2014; 9: 139–150.

59 Wilson R, Dowling RB, Jackson AD. The biology of bacterial colonization and invasion of the respiratory mucosa. *Eur Respir J* 1996; 9: 1523–1530.

60 Singanayagam A, Footitt J, Marczynski M, *et al.* Airway mucins promote immunopathology in virus-exacerbated chronic obstructive pulmonary disease. *J Clin Invest* 2022; 132: e120901.

61 Chen XS, Sun HY, Cheng XS, *et al.* Effect of eucalyptus on pulmonary function and oxidative stress in patients with acute exacerbation of pulmonary chronic obstructive pulmonary disease. *Prog Mod Biomed* 2018; 18: 1956–1959.

62 D'Elia C, Sechi F. Neltenexine *versus* carbocysteine in the treatment of exacerbations of mild chronic obstructive pulmonary disease: a randomized, controlled, open-label study. *Curr Ther Res Clin Exp* 2001; 62: 851–861.

63 Sharma A, Bagchi A, Gupta H, *et al.* Comparative evaluation of the efficacy, safety and tolerability of the fixed dose combinations of cefixime plus erdosteine and amoxicillin plus bromhexine in patients with acute exacerbations of chronic bronchitis. *Chest* 2007; 132: 529.

64 Finiguerra M, De Martini S, Negri L, *et al.* Clinical and functional effects of domiodol and sobrerol in hypersecretory bronchopneumonias. *Minerva Med* 1981; 72: 1353–1360.

65 Prabhu Shankar S, Chandrashekharan S, Bolmall CS, *et al.* Efficacy, safety and tolerability of salbutamol +guaiphenesin+bromhexine (Ascoril) expectorant versus expectorants containing salbutamol and either guaiphenesin or bromhexine in productive cough: a randomised controlled comparative study. *J Indian Med Assoc* 2010; 108: 313–320.

66 Bach PB, Brown C, Gelfand SE, *et al.* Management of acute exacerbations of chronic obstructive pulmonary disease: a summary and appraisal of published evidence. *Ann Intern Med* 2001; 134: 600–620.

67 Dobler CC, Morrow AS, Beuschel B, *et al.* Pharmacologic therapies in patients with exacerbation of chronic obstructive pulmonary disease: a systematic review with meta-analysis. *Ann Intern Med* 2020; 172: 413–422.

68 Jiang C, Zou J, Lv Q, *et al.* Systematic review and meta-analysis of the efficacy of N-acetylcysteine in the treatment of acute exacerbation of chronic obstructive pulmonary disease. *Ann Palliat Med* 2021; 10: 6564–6576.

69 Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease 2022 report. https://goldcopd.org/2022-gold-reports-2/ Date last accessed: 4 July 2022.

70 Wedzicha JEC-C, Miravitlles M, Hurst JR, *et al.* Management of COPD exacerbations: a European Respiratory Society/American Thoracic Society guideline. *Eur Respir J* 2017; 49: 1600791.

71 Yang I, Dabscheck E, George J, *et al.* The COPD-X Plan: Australian and New Zealand Guidelines for the management of Chronic Obstructive Pulmonary Disease 2021. https://copdx.org.au/wp-content/uploads/2021/04/COPDX-V2-63-Feb-2021_FINAL-PUBLISHED.pdf Date last accessed: 4 July 2022.

72 National Institute for Health and Care Excellence. Chronic obstructive pulmonary disease in over 16s: diagnosis and management. www.nice.org.uk/guidance/ng115/chapter/Recommendations. Date last accessed: 4 July 2022. Date last updated: 26 July 2019.

73 Lindenauer PK, Pekow P, Gao S, *et al.* Quality of care for patients hospitalized for acute exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med* 2006; 144: 894–903.

74 Murio C, Soler X, Pérez M, *et al.* Acute exacerbation of chronic obstructive pulmonary disease in primary care setting in Spain: the EPOCAP study. *Ther Adv Respir Dis* 2010; 4: 215–223.

75 Mathioudakis AG, Sivapalan P, Papi A, *et al*. The DisEntangling Chronic Obstructive pulmonary Disease Exacerbations clinical trials NETwork (DECODENET): rationale and vision. *Eur Respir J* 2020; 56: 2000627.