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Impact of Mucolytic Agents on COPD Exacerbations: A Pair-wise and Network Meta-analysis

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ABSTRACT
Mucolytics are potentially useful for the management of chronic obstructive pulmonary disease (COPD), although there is conflicting advice on their use in different guideline documents. Furthermore, there is paucity of data comparing the efficacy of the different mucolytic agents in reducing the odds of COPD exacerbations. We performed pair-wise and network meta-analyses to evaluate the impact of mucolytics in COPD. Randomized clinical trials lasting at least 3 months and investigating the effects of mucolytics on COPD exacerbations were identified from published studies and repository databases. Mucolytics significantly reduced the number of exacerbation vs. placebo (11 studies analyzed: odds ratio (OR) 0.51, 95% confidence interval (CI) 0.39–0.67; p < 0.001). The most effective drugs were carbocysteine, erdosteine, and N-acetylcysteine 1,200 mg/day (SUCRA 68.0–79.0%), whereas the OR was similar to placebo for ambroxol and N-acetylcysteine 600 mg/day. Only N-acetylcysteine 1,200 mg/day significantly protected against exacerbations vs. placebo (2 studies analyzed: OR 0.56, 95% CI 0.35–0.92; p < 0.05; high quality of evidence). A signal of effectiveness was detected for carbocysteine (2 studies analyzed: OR 0.45, 95% CI 0.20–1.01; p ≥ 0.05; moderate quality of evidence). Specific differences in study designs and patient-related characteristics, such as history of exacerbations and ethnicity, were potential effect modifiers for our statistical models, whereas neither respiratory function nor the use of corticosteroids influenced the analysis. This meta-analysis demonstrates that mucolytics are useful in preventing COPD exacerbations as maintenance add-on therapy to patients with frequent exacerbations. The effectiveness of mucolytics is independent of the severity of airway obstruction and the use of inhaled corticosteroids.

Introduction
The 2017 version of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy states that in “in COPD patients not receiving inhaled corticosteroids, regular treatment with mucolytics such as carbocysteine and N-acetylcysteine (NAC) may reduce exacerbations and modestly improve health status” (1). However, currently available data do not permit to assess the real target population for mucolytic agents because of the heterogeneity of chronic obstructive pulmonary disease (COPD) patients enrolled in the studies, doses of treatments, and concomitant medications (1,2).

A number of national and international bodies have recognized the potential utility of mucolytics in the management of stable COPD, although wide variability in their use exists, as evidenced by examining the national guidelines for management of COPD in Europe (3–6).

In order to shed light on a very controversial topic, a recent Cochrane meta-analysis aimed to establish whether treatment with mucolytics reduces frequency of exacerbations and/or days of disability in patients with chronic bronchitis or COPD demonstrated that mucolytics reduce the number of exacerbations by a small amount, and do not appear to cause any harm (2). The reduction was approximately one fewer exacerbation every three years. Remarkably, one person out of eight may avoid having an exacerbation, provided all take treatment every day for an average of 10 months.

These findings are definitely interesting, but they have been obtained by comparing active agents vs. placebo. Consequently, we have evidence that mucolytics as a class are potentially useful, but we still do not know if there is a mucolytic agent that is more effective than others in reducing frequency of exacerbations, also because head-to-head comparisons are lacking. This lack of information may explain why the choice of the mucolytic agent to be used is difficult and remains empiric, and likely why there are so many conflicting opinions on the use of these agents.

Pooling of direct and indirect evidence from randomized clinical trials (RCTs), known as mixed treatment comparisons (also called network meta-analysis), is becoming increasingly common in the clinical literature. A network meta-analysis allows coherent judgments on which of the several treatments is the most effective and produces estimates of the relative effects of each treatment compared with every other treatment in a network (7). Therefore, considering the confounding divergences on the use of mucolytics in the treatment of stable COPD in different national and international guidelines and strategies (3,8), the positive outcome of the Cochrane meta-analysis (2), and the lack of head-to-head RCTs of treatment interventions, we carried out a treatment comparison by systematic

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review and synthesis on the currently available clinical evidence by using an initial pair-wise meta-analysis to evaluate the overall impact of mucolytic agents on COPD exacerbations, and then a network meta-analysis to compare different mucolytic agents.

Materials and methods

Searching strategy

This pair-wise and network meta-analysis has been registered in PROSPERO (registration number: CRD42016053762 available at http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016053762), and performed in agreement with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (Figure 1) (9). Furthermore, this synthesis satisfied all the recommended items reported by the PRISMA-P 2015 checklist (10).

We undertook a comprehensive literature search for RCTs evaluating the influence of mucolytic agents on the odds of exacerbations in patients suffering from COPD (not chronic bronchitis) confirmed by pulmonary function testing. Due to seasonal variation, it has been suggested that the evaluation

Figure 1. PRISMA flow diagram for the identification of studies included in the meta-analysis concerning the impact of mucolytic agents on COPD exacerbations (A). Diagram displaying the network of the five arms involved in the Bayesian analysis. The links between nodes indicate the direct comparisons between pairs of treatments. The numbers shown along the link lines indicate the number of COPD patients comparing pairs of treatments head-to-head (B).
of COPD exacerbation should require a period of ≥ 1 year (11,12). However, since the rate of exacerbation was successfully investigated in studies with 3 months of follow-up (13), in this meta-analysis, we included RCTs lasting at least 3 months.

The identification of mucolytic agents was performed in agreement with GOLD 2014 and the American College of Chest Physicians and Canadian Thoracic Society Guideline for prevention of COPD exacerbations (14,15). In particular, the terms “ambroxol,” “carboxysteine,” “erodestone,” “iodinated glycerol,” and “N-acetylcysteine” were searched for the mucolytic agents, and the terms “chronic obstructive pulmonary disease” and “COPD” were searched for the disease. The search was performed in PubMed, Scopus, Embase, Google Scholar, and the repository database clinicaltrials.gov (16) through March 2017, to identify relevant studies published in the English language and published up to March 31, 2017. RCTs reporting the impact of oral mucolytic agents vs. placebo on COPD exacerbations have been included in the analysis.

Two reviewers independently checked the relevant RCTs identified from literature searches and databases. RCTs were selected in agreement with the previously mentioned criteria, and any difference in opinion about eligibility was resolved by consensus.

Quality score, risk of bias and evidence profile

The Jadad score, with a scale of 1 to 5 (score of 5 being the best quality), was used to assess the quality of the RCTs concerning the likelihood of biases related to randomization, double blinding, withdrawals, and dropouts (17). The risk of bias for each included study was also assessed via the Cochrane Collaboration’s tool (18). Two reviewers independently assessed the quality of individual studies, and any difference in opinion about eligibility was resolved by consensus.

The risk of publication bias was assessed by applying the funnel plot and Egger’s test through the following regression equation: \( \text{SND} = a + b \times \text{precision} \), where SND represents the standard normal deviation (treatment effect divided by its standard error (SE)), and precision represents the reciprocal of the standard error. Evidence of asymmetry from Egger’s test was considered to be significant at \( p < 0.1 \), and the graphical representation of 90% confidence bands is presented (17).

Meta-regression analysis was performed to examine the source of heterogeneity between studies, leading to asymmetry of funnel plot (19–21). Further analysis was carried out by using the meta-regression model to adjust for statistically significant \( (p < 0.05) \) confounders (22,23).

The quality of the evidence has been assessed in agreement with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system (24) overall for all the studies included in the synthesis, and for the subset meta-analyses.

Data extraction

Data from included studies were extracted from published papers, and/or online supplementary files, and/or the public database clinicaltrials.gov. Data extraction was carried out in agreement with the recommendations provided by the Cochrane Handbook for Systematic Reviews of Interventions (25). Data were extracted and checked for study characteristics and duration, doses of medications, patient characteristics, age, gender, smoking habits, FEV\(^1\), Jadad score, and number of exacerbations.

End points

The end point of this meta-analysis was to assess the protective effect of mucolytic drugs against COPD exacerbation, vs. placebo. In particular, we have measured the association between the treatment with mucolytic agent and COPD exacerbation. This allowed to evaluate the odds that a COPD exacerbation occurred in patients treated with mucolytic drugs, compared to the odds that a COPD exacerbation occurred in untreated patients (26).

Data analysis

We performed both pair-wise and network meta-analyses to evaluate the impact of mucolytic agents on COPD exacerbations. Since the follow-up duration was not consistent among the RCTs included in this meta-analysis, the data have been normalized as a function of person-season, where one season lasts 3 months (27–29). This method involved the conversion of the measures into a common metric (events per person-time) before meta-analyzing the data, leading to increased estimates of effect, precision, and clinical interpretability of results (25,30).

Results are expressed as odds ratio (OR) and 95% confidence interval (95%CI) in pair-wise meta-analysis. Since data were selected from a series of studies performed by researchers operating independently, and a common effect size cannot be assumed, we used the random-effects model to perform the pair-wise meta-analysis in order to balance the study weights and adequately estimate the 95%CI of the mean distribution of drugs effect on the investigated variable (27). In fact, although the mathematics behind the fixed-effects model are much simpler than those of the random-effects model, results of this quantitative synthesis cannot be generalized via fixed-effects model since the included studies were quite dissimilar (31), as reported in Table 1. Therefore, the greater the degree of difference among the studies incorporated in the analysis, the more important it becomes to employ the random-effects model (32).

A subset analysis was performed with regard to the effect of specific mucolytic drugs, doses, and quality of studies. High-quality studies were identified by considering the outcomes resulting from the summary of the Cochrane Collaboration’s tool and having Jadad score ≥ 3. Furthermore, a sensitivity analysis was carried out for studies that lasted ≥ 1 year compared with those that lasted < 1 year.

The network meta-analysis was performed to indirectly compare the effect of specific mucolytic drugs and doses. A full Bayesian evidence network was used (chains: 4; initial values scaling: 2.5; tuning iterations: 20.000; simulation iterations: 50.000; tuning interval: 10), and the convergence diagnostics for consistency and inconsistency was assessed via the Brooks-Gelman-Rubin method, as previously reported (33). Due to the characteristics of parameters besides the available data, the proper non-informative distributions specified the
<table>
<thead>
<tr>
<th>Study, year and reference</th>
<th>Trial Number Identifier</th>
<th>Study characteristics</th>
<th>Study duration (weeks)</th>
<th>Analysed patients</th>
<th>Drugs and daily doses</th>
<th>Exacerbation rates (treatment/placebo)</th>
<th>Disease characteristics</th>
<th>Age (years)</th>
<th>Male (%)</th>
<th>Current smokers (%)</th>
<th>Smoking history (pack-years)</th>
<th>Post-bronchodilator FEV1 (%) predicted</th>
<th>Jadad score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zheng et al. 2014 (42)</td>
<td>ChiCTR-TRC-09000460</td>
<td>Multicentre, prospective, randomized, double-blind, placebo-controlled, parallel groups</td>
<td>52</td>
<td>964</td>
<td>N-acetylcysteine, 1200 mg</td>
<td>0.26/0.33</td>
<td>COPD, GOLD II-IV</td>
<td>66.3</td>
<td>81.9</td>
<td>17.8</td>
<td>36.2</td>
<td>48.9</td>
<td>4</td>
</tr>
<tr>
<td>Tse et al. 2013 (43)</td>
<td>NCT01136239</td>
<td>Double-blind, randomized placebo-controlled</td>
<td>52</td>
<td>108</td>
<td>N-acetylcysteine, 1200 mg</td>
<td>0.24/0.43</td>
<td>COPD, GOLD I-IV</td>
<td>70.9</td>
<td>93.3</td>
<td>23.3</td>
<td>NA</td>
<td>59.6</td>
<td>4</td>
</tr>
<tr>
<td>Schermer et al. 2009 (44)</td>
<td>NA</td>
<td>Double-blind, randomized, double dummy, placebo-controlled</td>
<td>156</td>
<td>108</td>
<td>N-acetylcysteine, 600 mg</td>
<td>0.15/0.34</td>
<td>COPD, GOLD I-IV</td>
<td>59.4</td>
<td>72.9</td>
<td>53.6</td>
<td>27.3</td>
<td>69.8</td>
<td>4</td>
</tr>
<tr>
<td>Zheng et al. 2008 (48)</td>
<td>UMIN-CRT C000000233</td>
<td>Multicentre, randomized, double-blind, placebo-controlled, parallel-group</td>
<td>52</td>
<td>707</td>
<td>Carboxyline, 1500 mg</td>
<td>0.23/0.31</td>
<td>COPD, GOLD II-IV</td>
<td>65.2</td>
<td>78.5</td>
<td>74.5 (ever smokers)</td>
<td>NA</td>
<td>44.5</td>
<td>5</td>
</tr>
<tr>
<td>Bachh et al. 2007 (46)</td>
<td>NA</td>
<td>Single-blind, randomized, placebo-controlled study</td>
<td>16</td>
<td>100</td>
<td>N-acetylcysteine, 600 mg</td>
<td>0.56/0.83</td>
<td>COPD, GOLD II-III</td>
<td>61.4</td>
<td>78.0</td>
<td>NA</td>
<td>44.1</td>
<td>51.7</td>
<td>1</td>
</tr>
<tr>
<td>Tatsumi et al. 2007 (49)</td>
<td>NA</td>
<td>Multicentre, randomized, parallel-group</td>
<td>52</td>
<td>142</td>
<td>Carboxyline, 1500 mg</td>
<td>0.07/0.25</td>
<td>COPD, FEV1 &lt; 70%</td>
<td>70.2</td>
<td>91.5</td>
<td>NA</td>
<td>NA</td>
<td>&lt;70</td>
<td>1</td>
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<tr>
<td>Yaruda et al. 2006 (50)</td>
<td>NA</td>
<td>Randomized, double-blind, controlled trial</td>
<td>52</td>
<td>156</td>
<td>Carboxyline, 1500 mg</td>
<td>0.13/0.35</td>
<td>COPD, GOLD I-III</td>
<td>72.7</td>
<td>85.3</td>
<td>NA</td>
<td>44.3</td>
<td>61.5</td>
<td>3</td>
</tr>
<tr>
<td>Decramer et al. 2005 (45)</td>
<td>NA</td>
<td>Double-blind, placebo-controlled, parallel groups</td>
<td>156</td>
<td>354</td>
<td>N-acetylcysteine, 600 mg</td>
<td>0.33/0.33</td>
<td>COPD, GOLD II-III</td>
<td>62.0</td>
<td>77.0</td>
<td>44.0</td>
<td>NA</td>
<td>57.0</td>
<td>4</td>
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<tr>
<td>Moretti et al. 2004 (51)</td>
<td>NA</td>
<td>Multicentre, randomized, double-blind, placebo-controlled, parallel-group</td>
<td>32</td>
<td>124</td>
<td>Erdosteine, 600 mg</td>
<td>0.35/0.52</td>
<td>COPD, FEV1 &lt; 70%</td>
<td>67.5</td>
<td>79.9</td>
<td>32.9</td>
<td>&gt;20</td>
<td>59.2</td>
<td>3</td>
</tr>
<tr>
<td>Malerba et al. 2004 (52)</td>
<td>NA</td>
<td>Multicentre, randomized, double-blind, placebo-controlled, parallel-group</td>
<td>52</td>
<td>234</td>
<td>Ambroxol, 150 mg</td>
<td>0.11/0.12</td>
<td>COPD, FEV1 ≥ 60%, &lt;80%</td>
<td>60.6</td>
<td>72.6</td>
<td>32.9</td>
<td>NA</td>
<td>&lt;80</td>
<td>3</td>
</tr>
<tr>
<td>Pela et al. 1999 (47)</td>
<td>NA</td>
<td>Open, randomized, controlled</td>
<td>24</td>
<td>167</td>
<td>N-acetylcysteine, 600 mg</td>
<td>0.48/0.84</td>
<td>COPD, FEV1 &lt; 70%</td>
<td>66.0</td>
<td>75.7</td>
<td>24.0</td>
<td>NA</td>
<td>58.1</td>
<td>2</td>
</tr>
</tbody>
</table>

NA, not available.
prior densities, in agreement with the Bayesian Approaches to Clinical Trials and Health-Care Evaluation (34,35). Since the distributions were sufficiently vague, the reference treatment, study baseline effects, and heterogeneity variance were unlikely to have a noticeable impact on model results. In this condition, GeMTC software automatically generates and runs the required Bayesian hierarchical model and selects the prior distributions and starting values as well, via heuristically determining a value for the outcome scale parameter (i.e. outcome scale $S$) (36,37). The posterior mean deviance of data points in the unrelated mean effects model were plotted against their posterior mean deviation in the consistency model in order to provide information for identifying the loops in the treatment network where evidence was inconsistent (38). Results of the network meta-analysis are expressed as relative effect and 95% credible level (95% CI). The probability that each intervention arm was the most effective was calculated by counting the proportion of iterations of the chain in which each intervention arm had the highest mean difference, and the surface under the cumulative ranking curve (SUCRA), representing the summary of these probabilities, was also calculated. The SUCRA is 100% when a treatment is certain to be the best, and 0% when a treatment is certain to be the worst (33,39).

The optimal information size (OIS) was calculated as previously described (40), and the statistical significance was assessed for $p < 0.05$.

OpenMetaAnalyst (41) and GeMTC (36) software were used for performing the meta-analysis, SPSS Statistics (NY, US) for meta-regression, GraphPad Prism (CA, US) software for graphing the data, and GRADEpro for assessing the quality of evidence (24). The statistical significance was assessed for $p < 0.05$, and moderate to high levels of heterogeneity were considered for $I^2 > 50%$.

Results

Studies characteristics

Results obtained from 3,164 COPD patients (1,587 treated with a mucolytic agent, 1,577 treated with placebo) were selected from 11 published studies, including 6 RCTs on NAC (42–47), 3 on carbocysteine (48–50), one on erdosteine (51), and one on ambroxol (52) (Table 1). Eight RCTs, including 7 full papers (42–45, 48, 51, 52) and a correspondence (50), had a Jadad score ≥ 3. The risk of bias for each included study calculated via Jadad score was consistent with that assessed via the Cochrane Collaboration’s tool (Table 2). The period of treatment ranged from 16 to 156 weeks. Table 3 shows the definition of exacerbation as reported by the studies included in the synthesis.

Pair-wise meta-analysis

Treatment with mucolytic agents significantly reduced the odds of COPD exacerbations vs. placebo (11 studies analyzed: OR 0.51, 95% CI 0.39–0.67; $p < 0.001$) (Figure 2A). The sensitivity analysis identified greater effectiveness of mucolytics agents in studies lasting ≥ 1 year vs. shorter RCTs (OR 0.61, 95% CI 0.47–0.79 vs. OR 0.29, 95% CI 0.14–0.60, respectively). The subset analysis performed by including in the synthesis exclusively high-quality studies indicated that only the treatment with NAC administered at high dose (1,200 mg/day) significantly protected COPD patients against exacerbations (2 high-quality studies analyzed: OR 0.56, 95% CI 0.35–0.92), whereas NAC at lower dose (600 mg/day) did not significantly improve the odds of COPD exacerbations vs. placebo (2 high-quality studies analyzed: OR 0.95, 95% CI 0.85–1.07; $p ≥ 0.05$) (Figure 2B). Carbocysteine did not significantly reduce the exacerbation frequency vs. placebo (2 high-quality studies analyzed: OR 0.45, 95% CI 0.20–1.01; $p ≥ 0.05$); however, a signal of effectiveness was detected for this medication since the higher CI of the effect estimate only slightly overlapped the OR of 1 (no effect) (Figure 2B). The subset pair-wise meta-analysis for erdosteine and ambroxol was not carried out since only one high-quality RCT was identified for each drug (51,52).

Network meta-analysis

The ranking plot resulting from the network meta-analysis carried out on high-quality studies identified two distinct clusters of effectiveness. Specifically, carbocysteine, erdosteine, and NAC high-dose were effective drugs in reducing COPD exacerbations, whereas ambroxol and NAC at low dose were less-effective medications (Figure 2C). The SUCRA values of the effective medications ranged from 68.0% to 79.0%, whereas similar values to placebo were detected for both ambroxol and NAC at low dose (Table 4).

Bias and quality of evidence

A substantial level of heterogeneity was detected in the pair-wise meta-analysis ($I^2 91%, p < 0.001$), whereas the assessment of statistical consistency of the network meta-analysis indicated that all the points fit adequately with the line of equality ($R^2 0.99$; slope 0.96, 95%CI 0.95–0.97).

### Table 2. Summary of the risk of bias for each included study assessed via the Cochrane Collaboration’s tool (18).

<table>
<thead>
<tr>
<th>Study</th>
<th>Selection</th>
<th>Performance</th>
<th>Detection</th>
<th>Attrition</th>
<th>Reporting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zheng et al. 2014 (42)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>Tse et al. 2013 (43)</td>
<td>?</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>+</td>
</tr>
<tr>
<td>Schermer et al. 2009 (44)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>+</td>
</tr>
<tr>
<td>Zheng et al. 2008 (48)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>+</td>
</tr>
<tr>
<td>Bachh et al. 2007 (46)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>Tatsumi et al. 2007 (49)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>Yasuda et al. 2006 (50)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>Decramer et al. 2005 (45)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>Moretti et al. 2004 (51)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>Malerba et al. 2004 (52)</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>Pela et al. 1999 (47)</td>
<td>?</td>
<td>−</td>
<td>−</td>
<td>?</td>
<td>+</td>
</tr>
</tbody>
</table>

...
Table 3. Definition of COPD exacerbations as reported by studies included in the meta-analysis.

<table>
<thead>
<tr>
<th>Study, year and reference</th>
<th>Definition of COPD exacerbation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zheng et al. 2014 (42)</td>
<td>At least a 2 day persistence of two (type II moderate) or all three (type III, severe) major symptoms (worsening dyspnoea, increase in sputum purulence or volume), or of any one major symptom plus at least one minor symptom (type I, mild) (upper airway infection, unexplained fever, and increased wheezing).</td>
</tr>
<tr>
<td>Tse et al. 2013 (43)</td>
<td>“Two of the following three symptoms: increase in shortness of breath, volume, or purulence of sputum.”</td>
</tr>
<tr>
<td>Schermer et al. 2009 (44)</td>
<td>“At least 2-day persistence of at least two major symptoms (worsening dyspnoea and an increase in sputum volume, purulence, or both), or of any single major symptom plus more than one minor symptom (upper airway infection, unexplained fever, and increased wheezing).”</td>
</tr>
<tr>
<td>Zheng et al. 2008 (48)</td>
<td>“At least 2-day persistence of at least two major symptoms (worsening dyspnoea and an increase in sputum volume, purulence, or both), or of any single major symptom plus more than one minor symptom (upper airway infection, unexplained fever, and increased wheezing).”</td>
</tr>
<tr>
<td>Bachh et al. 2007 (46)</td>
<td>“Increased dyspnea and/or cough associated with a change in quality and quantity of sputum, which led the patient to seek medical attention and lasting for &gt; 3 days.”</td>
</tr>
<tr>
<td>Tatsumi et al. 2007 (49)</td>
<td>“Changes in the following symptoms from their stable condition according to the Anthonisen criteria: dyspnea, sputum purulence, sputum volume, cold, wheeze, cough, fever, and change in respiratory rate or heart rate of 20%.”</td>
</tr>
<tr>
<td>Yasuda et al. 2006 (50)</td>
<td>“An acute and sustained worsening of COPD symptoms requiring changes to regular treatment, as previously described.”</td>
</tr>
<tr>
<td>Decramer et al. 2005 (45)</td>
<td>“Increase in dyspnoea, cough, or both associated with a change in quality and quantity of sputum, which led the patient to seek medical attention and which lasted for at least 3 days.”</td>
</tr>
<tr>
<td>Moretti et al. 2004 (51)</td>
<td>“New episodes of acute disease with mucopurulent or purulent sputum, cough and at least two of the following symptoms: general malaise, fever &gt; 38°C, breathlessness, difficulty in expectoration and leukocytosis. The same definition was used for exacerbations occurring before and during the trial.”</td>
</tr>
<tr>
<td>Malerba et al. 2004 (52)</td>
<td>“A concomitance of purulent mucus plus at least one of the following: fever ≥ 38°C, general malaise, dyspnea, difficult expectoration, or leukocytosis (leukocytes count above upper normal value at a clinically significant degree and when previously within normal range at the screening visit).”</td>
</tr>
<tr>
<td>Pela et al. 1999 (47)</td>
<td>“The worsening of the clinical profile of the patient with increased cough, dyspnoea and expectoration with mucopurulent sputum, with or without fever requiring medical intervention.”</td>
</tr>
</tbody>
</table>

Overall, the cumulative number of enrolled COPD patients in the studies reached the OIS for a binary outcome meta-analysis on mucolytic agents (OIS: 414; delta: +2,750). Specifically, OIS was reached for carbocysteine (OIS: 210; delta: +795), NAC high-dose (OIS: 502; delta: +570), and NAC low-dose (OIS: 380; delta: +349), whereas the number of patients in the studies on ambroxol (OIS: >5,000; delta: <−5,000) and erdosteine (OIS: 310; delta: −186) did not meet the OIS criteria.

The analysis performed via funnel plot and Egger’s tests indicated that smaller studies may have significantly ($p < 0.1$) distorted the results of this meta-analysis because of inflated estimates of effect size for both the overall pair-wise meta-analysis on mucolytic agents (Figure 3A and B) and the subset analysis on carbocysteine (Figure 3C and D). On the contrary, no significant ($p ≥ 0.1$) publication bias was detected for NAC (Figure 3E and F). Results of Egger’s test should be interpreted with caution.
Table 4. SUCRA values for the impact of mucolytic agents in reducing the odds of COPD exacerbations.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>SUCRA (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ambroxol</td>
<td>33.2</td>
</tr>
<tr>
<td>Carbocysteine</td>
<td>79.0</td>
</tr>
<tr>
<td>Erdosteine</td>
<td>70.4</td>
</tr>
<tr>
<td>N-acetylcysteine high-dose</td>
<td>68.0</td>
</tr>
<tr>
<td>N-acetylcysteine low-dose</td>
<td>26.0</td>
</tr>
<tr>
<td>Placebo</td>
<td>24.0</td>
</tr>
</tbody>
</table>

SUCRA: surface under the cumulative ranking curve

in case of insufficient number of studies, due to the low power of 10 or fewer RCTs for meta-analyses (53). The analysis of publication bias for erdosteine and ambroxol was not carried out since only one RCT was identified for each drug (51,52).

The meta-regression model indicated that several explanatory variables might have influenced the size of intervention effect. The characteristics of the studies, such as duration and quality, and the history of exacerbation rate before patients were enrolled into the RCTs, are potential effect modifiers that may have significantly ($p < 0.05$) altered the impact of mucolytic drugs on the frequency of COPD exacerbations. A signal ($p = 0.065$) of effect modifier was detected also for ethnicity, with Chinese COPD patients being less responsive to the protective effect of mucolytic agents compared with non-Chinese populations. However, neither respiratory function nor the use of corticosteroids represented significant modifier covariates ($p \geq 0.05$). Detailed results on meta-regression analysis are reported in Figure 4. After adjusting for the significant confounders detected in the meta-regression model, therapy with mucolytic agents remained as a statistically significant treatment against COPD exacerbations (nonadjusted $p < 0.001$; adjusted for Jadad score $p < 0.001$).

The GRADE approach indicated moderate quality of evidence for the overall impact of mucolytic agents on the odds of COPD exacerbation. The GRADE subset analysis of specific mucolytic agents is reported in Table 5.

![Figure 3](image-url)  
**Figure 3.** Publication bias assessment via funnel plots (left panels) and Egger’s test (right panels) for the impact of mucolytic agents (A and B) on the rate of COPD exacerbations vs. placebo, and subset analysis of carbocysteine (C and D) and N-acetylcysteine (E and F). SND, standard normal deviate. *$p < 0.1$.**
Figure 4. Meta-regression analysis for study and publication characteristics (A–C), disease characteristics (D–F), ethnicity (G) and corticosteroid therapy (H and I). The lower the log odds ratio the greater the treatment effect on reduction of COPD exacerbations. FEV₁, forced expiratory volume in 1 second; ICS, inhaled corticosteroids; CS, corticosteroids. "p < 0.05: significant interaction between the treatment with mucolytic drugs vs. exacerbation rate and the potential modifier covariates.

Discussion

The results of this meta-analysis demonstrate that mucolytic drugs are effective in protecting patients against COPD exacerbations, and that this beneficial effect was greater in patients treated for one year or longer. Carbocysteine, erdosteine, and NAC administered at high dose (600 mg twice daily, corresponding to 1,200 mg/day) were the most effective agents, whereas neither ambroxol nor NAC administered at low dose (600 mg/day) reduced the odds of COPD exacerbations, compared with placebo.

NAC high-dose elicited a significant protective effect against COPD exacerbations among the most effective compounds, as supported by GRADE analysis, and a signal of effectiveness was detected for carbocysteine. Small studies on carbocysteine, such as those conducted by Tatsumi et al. [49] and Yasuda et al. [50], were characterized by low-quality according to the Jadad score, and elicited the so called "small study effect", in which the treatment effect estimate was greater than that observed in larger and well-designed studies. Although only one RCT on erdosteine was eligible to be included in this synthesis (51), the network approach permitted a comparison of the efficacy of this medication with the other mucolytic agents. Erdosteine was within the cluster of the most effective drugs, regardless of the level of evidence.

Indeed, this meta-analysis reports substantial level of heterogeneity. Nevertheless, distribution of I² values of 509 meta-analyses in the Cochrane Database of Systematic Reviews showed that about a quarter of meta-analyses had I² values over 50%, and that that the distribution of heterogeneity was roughly flat even for I² ≈ 90% (54). Moreover, the quantification of heterogeneity is only one component of a wider investigation of variability across studies, and the importance of I² values depends also on direction of effects (54). Thus, heterogeneity of this quantitative synthesis should be interpreted considering that most of the estimates showed the same direction of effect toward protective impact of mucolytic agents against COPD exacerbations.

Actually, NAC did not reach the suggested minimal clinical important difference (MCID) of 22% reduction in exacerbation rate (12,55). However, the GRADE analysis indicated a
95% probability of up to 17.8% risk reduction of COPD exacerbations in patients treated with high-dose NAC compared with placebo. This finding is intriguing, but it must be pointed out that mucolytic drugs were administered as add-on to standard COPD therapy in all the high-quality RCTs that have been included in this meta-analysis, suggesting that their beneficial protective role may be additive to that already elicited by standard therapy for COPD.

The definition of COPD exacerbation was assessed by a clinical point of view in all studies included in this meta-analysis, whereas little importance was given to the duration of symptoms. Nevertheless, it must also be pointed out that the identification of a correct MCID for COPD exacerbations is difficult because of the lack of a uniform clinical definition and the commonly underreported frequency and severity of exacerbations, which are potential targets for intervention (55). Interventions reducing exacerbations by as little as 11% appear to be regarded widely as clinically important (56). Thus, NAC high-dose may even reach the MCID for COPD exacerbations if the studies that have influenced the 2017 GOLD recommendations are considered. (56).

Referring to the recent findings of a previous meta-analysis by our group (27), the 2017 GOLD recommendations indicated that regular treatment with mucolytics may reduce COPD exacerbations and improve health status (1). The GOLD 2017 document cited also a Cochrane review (2) to recommend the use of mucolytic agents only in COPD patients not receiving inhaled corticosteroids, and to report that due to the heterogeneity of study populations, treatment dosing and concomitant treatments, currently available data do not allow one to identify precisely the potential target population for this class of drugs (1). Probably the conclusions of the Cochrane review (2) have been misunderstood, since the authors stated that mucolytics may be considered as (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 as (2) add-on treatment once all other therapies to reduce exacerbations have been utilized (2).

The present meta-analysis updates the data analyzed by Poole and colleagues (2). Our network approach allowed the efficacy of the specific mucolytic agents to be ranked, and we also considered the quality of evidence, focusing on high-quality RCTs. Moreover, we used for the first time a meta-regression to identify the explanatory variables that influence the effect size of the interventions. The concomitant use of corticosteroids, administered either systemically or via inhalation, did not modify the effectiveness of mucolytic agents with regard to COPD exacerbations. Furthermore, mucolytics were more effective in frequent exacerbators, and the extent of bronchial obstruction was not a confounder. Furthermore, the meta-regression analysis further confirms that the quality of RCTs is a relevant effect modifier. In any case, the identified confounders did not alter the findings reported in this quantitative synthesis, since adjusting for the significant mediators confirmed the protective effect of mucolytic agents against COPD exacerbations.

The current international guidelines for COPD do not differentiate treatment options for any drug class based on potential treatments.
ethnical differences (57). However, since the only well-designed RCTs that have documented an effect for NAC or carbocysteine on COPD exacerbations (HIACE, PANTHEON and PEACE) were performed in China (42,43,48), it is difficult to say whether this is a true ethnicity effect, or a local study effect. The findings of this study indicate that a specific population effect may exist but, unexpectedly, it seems that Chinese patients are less responsive to the protective effect of mucolytic agents compared with non-Chinese populations, suggesting that the impact of mucolytic drugs may be greater in the Caucasian populations.

A meta-analysis provides only the effect estimates that, by definition, reflect an estimate of the possible impact of the intervention on the investigated outcome(s) and, in any case, result by indirect comparisons. Therefore, the real impact of the most effective mucolytic drugs should be confirmed by performing well-designed head-to-head and placebo-controlled RCTs.

It is unlikely that comparative pragmatic RCTs in the field of respiratory research will be performed, due to their cost and lack of interest of pharmaceutical companies (17). However, a well-powered RCT that will directly compare the efficacy of carbocysteine, erdosteine, and NAC is highly desirable. Furthermore, pre-clinical studies may help to understand if the mechanism of action leading to the protective effect of mucolytics is specific for each compound, as demonstrated for NAC in a validated ex vivo model of COPD exacerbation (58), or if it is an effect of class.

Concluding, this quantitative synthesis supports the use of mucolytic drugs as add-on therapy to prevent COPD exacerbations, especially when administered to patients with frequent exacerbations. The effectiveness of mucolytics seems to be independent of the level of bronchial obstruction and the use of corticosteroids. Consequently, mucolytic agents should be offered to GOLD group C and group D patients. However, results of further RCTs are needed to improve the quality of evidence of most of the analyzed mucolytic agents, in order to correctly rank their effectiveness and suggest their use in these COPD patients.

Conflict of interest

MC has participated as a lecturer, speaker, and advisor in scientific meetings and courses under the sponsorship of Almirall, AstraZeneca, Bio Futura, Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline, Menarini Group, Lallemand, Mundipharma, Novartis, Pfizer, Verona Pharma, and Zambon, and has been a consultant to Chiesi Farmaceutici, Lallemand, Novartis, Verona Pharma, and Zambon. His department was funded by Almirall, Boehringer Ingelheim, Novartis, and Zambon.

PR participated as a lecturer, speaker, and advisor in scientific meetings and courses under the sponsorship of Almirall, AstraZeneca, Bio Futura, Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline, Menarini Group, Mundipharma, and Novartis. His department was funded by Almirall, Boehringer Ingelheim, Novartis, and Zambon.

LC has participated as advisor in scientific meetings under the sponsorship of Boehringer Ingelheim, received non-financial support by AstraZeneca, received a research grant partially funded by Boehringer Ingelheim, Novartis and Almirall, and has been a consultant to Zambon and Verona Pharma. His department was funded by Almirall, Boehringer Ingelheim, Novartis, and Zambon.

NAH served as a consultant to Boehringer Ingelheim GmbH, Sunovion Pharmaceuticals Inc, Novartis AG, Mylan Inc, Pearl Therapeutics Inc, and Pfizer Inc. His institution received grant support on his behalf from GlaxoSmithKline plc, Boehringer Ingelheim GmbH, Pfizer Inc, Pearl Therapeutics Inc, and Sunovion Pharmaceuticals Inc.

MGM has participated as a lecturer, speaker, and advisor in scientific meetings and courses under the sponsorship of Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline and Novartis, and has been a consultant to Chiesi Farmaceutici.

Study registration

PROSPERO 2016:CRD42016053762

Author contributions

MC contributed to study conception and design; contributed to interpretation of data; drafted the submitted article, revised it critically for important intellectual content, and provided final approval of the version to be published; and has agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

PR contributed to study conception and design; contributed to acquisition and interpretation of data; revised the submitted article critically for important intellectual content, and provided final approval of the version to be published; and has agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

MGM and NAH contributed to study conception and design; contributed to interpretation of data; revised it critically for important intellectual content and provided final approval of the version to be published; and has agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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