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Use of mucolytics in COPD: A Delphi consensus study

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ABSTRACT

Background: International guidelines recommend mucolytic agents as add-on therapy in selected patients with COPD because they may reduce exacerbations and improve health status. As the evidence varies among mucolytic agents, we used the Delphi method to assess consensus amongst an international panel of COPD experts on mucolytics use in COPD.

Methods: 53 COPD experts from 12 countries were asked to complete an online questionnaire and rate their agreement with 15 statements using a 5-point scale. The mucolytic agents evaluated were carbocysteine, erdosteine and N-acetylcysteine (NAC). Data were collected anonymously and consensus presented using descriptive statistics.

Results: The 47 respondents reached consensus on the statements. They agreed that regular treatment with mucolytic agents effectively reduces the frequency of exacerbations, reduces the duration of mild-to-moderate exacerbations, and can increase the time to first exacerbation and symptom-free time in COPD patients. Consensus was consistently highest for erdosteine. The experts agreed that all three mucolytics display antioxidant and anti-inflammatory activity. Erdosteine and NAC were thought to improve the efficacy of some classes of antibacterial drugs. All three mucolytics were considered effective for the short-term treatment of symptoms of acute exacerbations when added to other drugs. The panel agreed that approved doses of mucolytic agents have favorable side-effect profiles and can be recommended for regular use in patients with a bronchitic phenotype.

Conclusions: Consensus findings support the wider use of mucolytic agents as add-on therapy for COPD. However, the differences in pharmacological actions and clinical effectiveness must be considered when deciding which mucolytic to use.

Abbreviations: BRONCUS, Bronchitis Randomized on NAC Cost-Utility Study; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 s; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroid; NAC, N-acetylcysteine; PANTHEON, Placebo-controlled study on efficAcy and safety of N-acetylcysTeine High dose in Exacerbations of chronic Obstructive pulmoNary disease; PEACE, Preventive Effects on Acute Exacerbations of COPD with Carbocysteine; RESTORE, Reducing Exacerbations and Symptoms by Treatment with ORal Erdosteine in COPD.

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1. Introduction

Preventing exacerbations of chronic obstructive lung disease (COPD) is one of the key goals of COPD treatment [1,2] because exacerbations can lead to a faster decline in lung function [3,4], poorer health status [5], hospitalization and increased mortality [6,7] and a significant burden on health care systems [7]. Treatments that effectively reduce the frequency, severity and/or duration of acute exacerbations of COPD may slow disease progression and improve patient prognosis [8].

Airway mucus hypersecretion and impaired mucus clearance usually manifest with chronic cough and sputum production (chronic bronchitis), which are associated with exacerbations and poor outcomes in patients with COPD [9–11].

Mucolytic agents licensed for use in patients with COPD include the thiol-based agents carbocysteine (5-carboxymethyl-L-cysteine), erdosteine, and N-acetylcysteine (NAC). Recent studies have indicated that patients with moderate COPD (spirometrically-defined as post-bronchodilator forced expiratory volume in 1 s [FEV_1] 50–79% predicted) benefit the most from treatment with mucolytics as add-on therapy [12,13].

The 2020 Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommends the regular use of mucolytic agents, because they may reduce exacerbations of COPD and modestly improve the health status, particularly in patients not taking inhaled corticosteroids (ICS) [1]. International guidelines recommend use of an oral mucolytic agent to prevent future exacerbations for COPD with moderate or severe airflow obstruction and exacerbations despite optimal inhaled therapy [2]. However, national guidelines for the management of COPD in Europe vary in their recommendations for use of mucolytics [14].

Although mucolytic agents are widely used by patients with COPD in everyday clinical practice [15,16], there have been no head-to-head clinical studies comparing the different thiol-based mucolytic agents which also exhibit antioxidant, anti-inflammatory, and antimicrobial activities that may contribute to their differential clinical effects [17].

The Delphi method is a widely used, structured process for achieving expert consensus and making group-based decisions, especially when high-quality evidence is lacking [18,19].

The purpose of this study was to use the Delphi method to survey an international panel of COPD experts to explore their views and clinical experience on the use of mucolytics in the treatment of COPD and to enable consensus development on this specific topic.

2. Methods

This Delphi study was conducted between June 2019 and January 2020. A panel of 53 experts on the treatment of COPD from 12 countries (Bulgaria, Czech Republic, Egypt, Greece, Israel, Italy, Portugal, Romania, Russia, Slovakia, Turkey, and the UK) was identified and invited by personal invitation letter to participate in the Delphi study. For each country, a Local Coordinator was enrolled, who in turn recruited the experts who were key opinion leaders of their country for their knowledge and experience in the treatment of COPD. All participants were chosen among pulmonologists and pharmacologists with a specific focus and extensive clinical expertise on COPD, with relevant experience as an author of scientific papers on COPD treatment and mucolytics.

The Delphi structure (Fig. 1) involved one round of data collection using a web-based questionnaire. Following acceptance to participate in the study, each Delphi panel member was invited to consult relevant literature on the field before they received the link to the web-based questionnaire.

The web-based questionnaire, available only in English, was developed and validated by the Project Scientific Reviewer (AP). Participants based their answers on their professional daily clinical practice and literature review. The questionnaire was completed anonymously and consisted of a series of 15 statements (Table 1). Each respondent was asked to rate his/her level of agreement with each statement using the following 5-point Likert scale: 1 = strongly disagree, 2 = disagree, 3 = agree, 4 = more than agree, and 5 = strongly agree. When evaluating each statement, participants were asked to consider the following

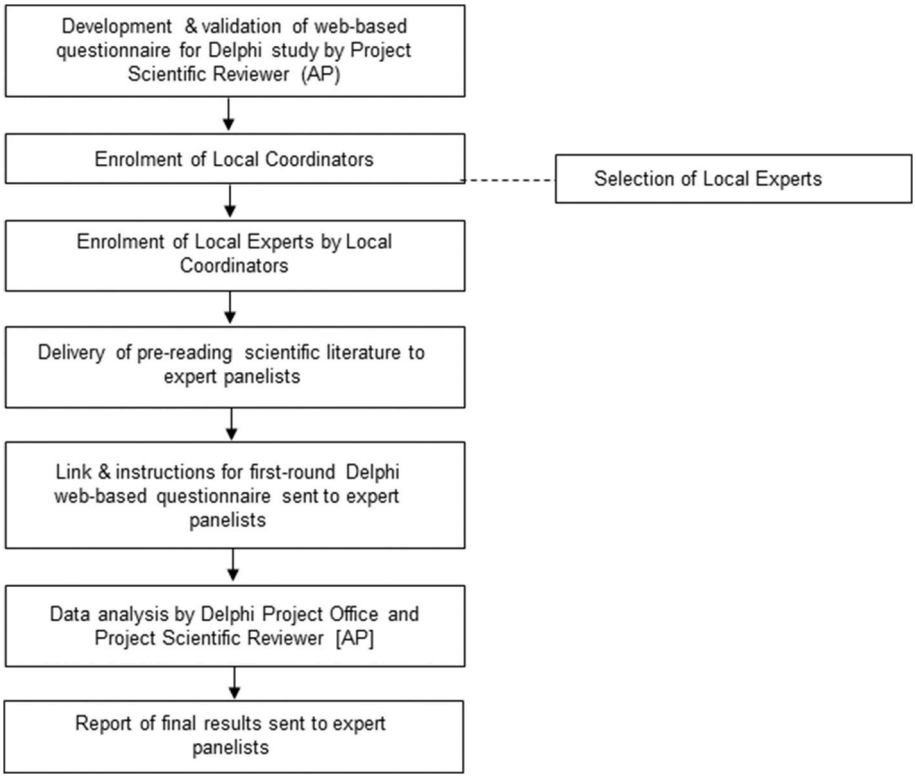

Fig. 1. Study design of the Delphi method.

Table 1
Results of the Delphi study statements for the 47 respondents.

Statement	Level of agreement[a], n					Consensus[b], %
	1	2	3	4	5	
1. Standard doses of mucolytics are useful in the treatment of chronic bronchitis and COPD	0	1	11	20	15	Positive, 98
2. Based on available data, the chronic use of mucolytic drugs at their standard doses is effective in reducing the frequency of exacerbations in patients with COPD						
2.1 NAC	0	12	18	16	1	Positive, 74
2.2 Erdosteine	0	1	7	13	26	Positive, 98
2.3 Carbocysteine	0	8	20	17	2	Positive, 83
3a. Besides their efficacy on mucus rheology and production, mucolytic drugs exhibit other pharmacological properties: Anti-inflammatory activity						
3.1a NAC	0	7	17	19	4	Positive, 85
3.2a Erdosteine	0	3	11	15	18	Positive, 94
3.3a Carbocysteine	0	11	26	8	2	Positive, 77
3b. Besides their efficacy on mucus rheology and production, mucolytic drugs exhibit other pharmacological properties: Antioxidant activity						
3.1b NAC	0	2	12	23	10	Positive, 96
3.2b Erdosteine	0	0	9	18	20	Positive, 100
3.3b Carbocysteine	0	5	23	15	4	Positive, 89
3c. Besides their efficacy on mucus rheology and production, mucolytic drugs exhibit other pharmacological properties: Can improve the efficacy of some classes of antibacterial drugs						
3.1c NAC	1	14	22	9	1	Positive, 68
3.2c Erdosteine	0	3	8	19	17	Positive, 94
3.3c Carbocysteine	1	19	21	6	0	No consensus
4. The duration of exacerbations (number of days/year) is as important as their frequency (number of events/year) in the evaluation of patient's COPD stage	0	5	6	16	20	Positive, 89
5. In my daily practice, mucolytics used at standard doses for up to 10 days are effective in treating symptoms of acute exacerbations in patients with COPD, in addition to other drugs						
5.1 NAC	0	8	15	19	5	Positive, 83
5.2 Erdosteine	0	3	9	17	18	Positive, 94
5.3 Carbocysteine	2	9	21	13	2	Positive, 77
6. When used regularly mucolytics can reduce the duration of each mild-to-moderate exacerbation in patients with COPD						
6.1 NAC	0	8	21	15	3	Positive, 83
6.2 Erdosteine	0	3	4	14	26	Positive, 94
6.3 Carbocysteine	1	11	22	11	2	Positive, 74
7. When used regularly mucolytics can increase the time to first exacerbation in patients with mild-to-moderate COPD						
7.1 NAC	0	13	15	16	3	Positive, 72
7.2 Erdosteine	0	3	5	17	22	Positive, 94
7.3 Carbocysteine	0	13	24	9	1	Positive, 72
8. When used regularly by patients with COPD mucolytics can increase the time free from symptoms disease						
8.1 NAC	0	8	19	14	6	Positive, 83
8.2 Erdosteine	0	5	5	19	18	Positive, 89
8.3 Carbocysteine	0	12	22	11	2	Positive, 74
9. Mucolytics are associated with a favorable side effect profile when used at approved doses						
9.1 NAC	1	3	7	16	20	Positive, 91
9.2 Erdosteine	2	1	3	10	31	Positive, 94
9.3 Carbocysteine	0	5	8	15	19	Positive, 89
10. In my clinical practice orally administered mucolytics, used as add-on therapy in COPD, are associated with a high level of patient adherence	0	4	14	14	15	Positive, 91
11. There are methods allowing to assess whether data resulting from meta analyses of clinical trials with mucolytics in patients with COPD provide high quality of evidence	0	2	13	22	10	Positive, 96
12. Data from meta-analyses of clinical trial with mucolytics support their efficacy in reducing the risk of hospitalization in patients with COPD						
12.1 NAC	0	7	21	16	3	Positive, 85
12.2 Erdosteine	0	0	7	18	22	Positive, 100
12.3 Carbocysteine	1	13	24	9	0	Positive, 70
13. When used regularly by patients with a bronchitic phenotype of COPD, mucolytics can effectively prevent mild-to-moderate exacerbations						
13.1 NAC	0	7	13	20	7	Positive, 85
13.2 Erdosteine	0	2	5	15	25	Positive, 96
13.3 Carbocysteine	0	8	18	18	3	Positive, 83
14. In my clinical practice, when used regularly by patients with a bronchitic phenotype of COPD, mucolytics can reduce symptoms such as cough and excessive mucus production						
14.1 NAC	0	6	13	19	9	Positive, 87
14.2 Erdosteine	0	1	5	19	22	Positive, 98
14.3 Carbocysteine	0	9	17	17	4	Positive, 81
15. There is sufficient evidence available to recommend the regular use of mucolytics in patients with a bronchitic phenotype of COPD						
15.1 NAC	0	7	19	13	8	Positive, 85
15.2 Erdosteine	0	2	9	14	22	Positive, 96
15.3 Carbocysteine	0	7	23	15	2	Positive, 85

Abbreviations: NAC, N-acetylcysteine.

[a] Level of agreement: 1 = strongly disagree, 2 = disagree, 3 = agree, 4 = more than agree, and 5 = strongly agree.

[b] Consensus reached when ≥66% of respondents gave a score of 1 or 2 (negative consensus) or ≥66% gave a score of 3, 4 or 5 (positive consensus). No consensus was reached if the sum of responses for negative consensus (1–2) or positive consensus (3–5) was <66%.

approved standard daily doses of mucolytics: carbocysteine 1500 mg, erdosteine 900 mg and NAC 600 mg (only in Turkey 1200 mg, high dose).

Consensus for each statement was defined *a priori* as at least 66% agreement of respondents [20]. A statement achieved consensus when ≥66% of respondents gave a score of 1 or 2 (negative consensus) or ≥66% gave a score of 3, 4 or 5 (positive consensus). No consensus was reached if the sum of responses for negative consensus (1–2) or positive consensus (3–5) was <66%.

If consensus was not reached for some of the statements at the first round, the Project Scientific Reviewer and the Local Coordinators were asked to decide whether to implement a second round of the questionnaire only for those statements where consensus was not reached, or to validate the outcomes reached at the first round. The majority rule was used for this decision.

2.1. Data analysis

No personal information was collected from the Delphi panel and all questionnaire responses were collated anonymously. Data were analyzed using the Delphi Ethos Personal Tool and reported as descriptive statistics.

3. Results

Of the 53 experts in the Delphi panel, 47 rated the statements in the online questionnaire, giving a response rate of 89%. Table 1 summarizes the results for these respondents and shows the consensus obtained for each statement of the questionnaire.

The majority (98%) of respondents agreed that standard doses of mucolytics are useful in the treatment of chronic bronchitis and COPD. Based on the available data, each of the three mucolytic agents was considered effective in reducing the frequency of exacerbations in patients with COPD when used long-term at standard doses (Fig. 2). The positive consensus among respondents was of 98% for erdosteine, 83% for carbocysteine, and 74% for NAC. In addition, 89% of respondents considered that duration of exacerbations was as important as the frequency of exacerbations when evaluating COPD stage.

There was a positive consensus that all three mucolytics have additional pharmacological properties of anti-inflammatory activity and

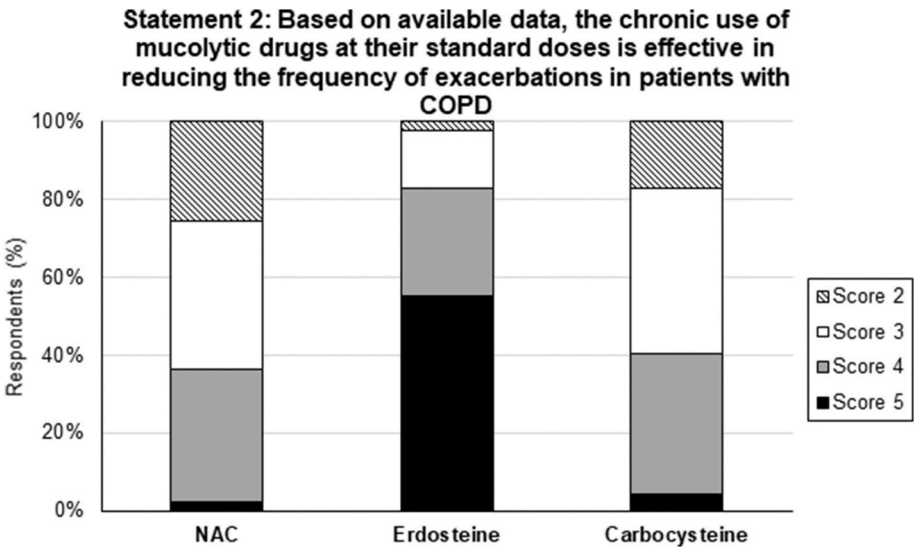

Fig. 2. Level of agreement for the mucolytic agents N-acetylcysteine (NAC), erdosteine and carbocysteine for Statement 2: Based on available data, the chronic use of mucolytic drugs at their standard doses is effective in reducing the frequency of exacerbations in patients with COPD. Number of respondents = 47. Score 1 = strongly disagree, 2 = disagree, 3 = agree, 4 = more than agree, and 5 = strongly agree.

antioxidant activity (Fig. 3a and b). The respondents also agreed that erdosteine and NAC can improve the efficacy of some classes of antibacterial drug but no consensus on this property was reached for carbocysteine during the first round questionnaire (Fig. 3c). The Scientific Committee (Project Scientific Reviewer and Local Coordinators) decided not to proceed with a second round questionnaire to reach a consensus for this statement.

Positive consensus was reached that short-term treatment for up to 10 days with standard doses of carbocysteine, erdosteine or NAC is effective at treating the symptoms of acute exacerbations when used in addition to other drugs (Statement 5, Table 1). There was also agreement that regular use of these mucolytics can reduce the duration of mild-to-moderate exacerbations (Fig. 4), increase the time to first exacerbation, and increase the time free from symptoms (Statements 7 and 8, Table 1). For each of these statements, the positive consensus was numerically greatest for erdosteine.

The respondents agreed that the three mucolytics have favorable side-effects profiles when used at approved doses and that there is a high level of patient adherence when mucolytics are used as add-on therapy in clinical practice (Statements 9 and 10, Table 1).

There was a positive consensus (96%) that methods are available to provide high-quality evidence from meta-analyses of clinical trials with mucolytics in patients with COPD. Also, the respondents agreed that data from meta-analyses support the efficacy of mucolytics in reducing the risk of hospitalization (Fig. 5). The positive consensus was 100% for erdosteine, 85% NAC, and 70% for carbocysteine.

The last three statements of the questionnaire focused on patients with a chronic bronchitis phenotype of COPD. For each of the three mucolytic agents, there was a positive consensus that they can effectively prevent mild-moderate exacerbations and reduce symptoms (e.g. cough, excessive mucus production) (Statements 13 and 14, Table 1), and can be recommended for regular use in patients with a bronchitic phenotype (Fig. 6).

4. Discussion

This Delphi study captured the opinions of a panel of international COPD experts from 12 different countries on various aspects of the use of mucolytics in the treatment of COPD. There was a high response rate (89%) and the results showed a broad positive consensus on the statements in the first round questionnaire, such that a second round of questions was not necessary.

There was a high level of consensus between the COPD experts on the properties of mucolytic agents and their efficacy and safety in the treatment of patients with COPD. Standard doses of mucolytics were considered useful in the treatment of chronic bronchitis and COPD by 98% of the respondents.

The Delphi panel of experts agreed that regular treatment with these mucolytic agents effectively reduces the frequency and duration of exacerbations, both important factors for staging COPD. Moreover, the respondents agreed that regular use of mucolytics can increase the time to first exacerbation and the time free from symptoms. There was a numerical trend in favor of erdosteine for all these outcomes. This expert opinion is supported by a *post hoc* analysis of the randomized, placebo-controlled RESTORE study [12], which found that the addition of erdosteine to usual maintenance therapy for 12 months in a subgroup of 254 patients with spirometrically-defined moderate COPD (post-bronchodilator FEV_1 50–79% predicted) significantly reduced the rate and duration of exacerbations and increased exacerbation-free time by 51 days. Thus, there is consensus among an international group of COPD experts that mucolytic agents are effective in reducing the overall burden of exacerbations when added to usual maintenance therapy for COPD. This supports data from a recent network meta-analysis, which demonstrated that mucolytic agents are useful in preventing exacerbations of COPD when used as add-on therapy in patients with frequent exacerbations [21].

Although consensus was reached on all 15 statements, the levels of agreement for each statement differed between the three mucolytic agents, suggesting that the panelists consider that there are differences between these mucolytic agents even in the absence of head-to-head comparative studies. Almost all respondents (96%) agreed that meta-analytic data provides high-quality evidence and there were high levels of agreement that meta-analytic data supports the efficacy of erdosteine (100%), NAC (85%), and carbocysteine (70%) in reducing the risk of hospitalization.

In this survey there was positive consensus that carbocysteine, erdosteine, and NAC exhibit antioxidant and anti-inflammatory activity. Although respondents agreed that erdosteine (94%) and NAC (68%) can improve the efficacy of some classes of antibacterial drugs, there was no consensus for carbocysteine on this topic. This conflicts with one study showing that carbocysteine administered in combination with amoxicillin resulted in increased antibiotic penetration into the bronchial

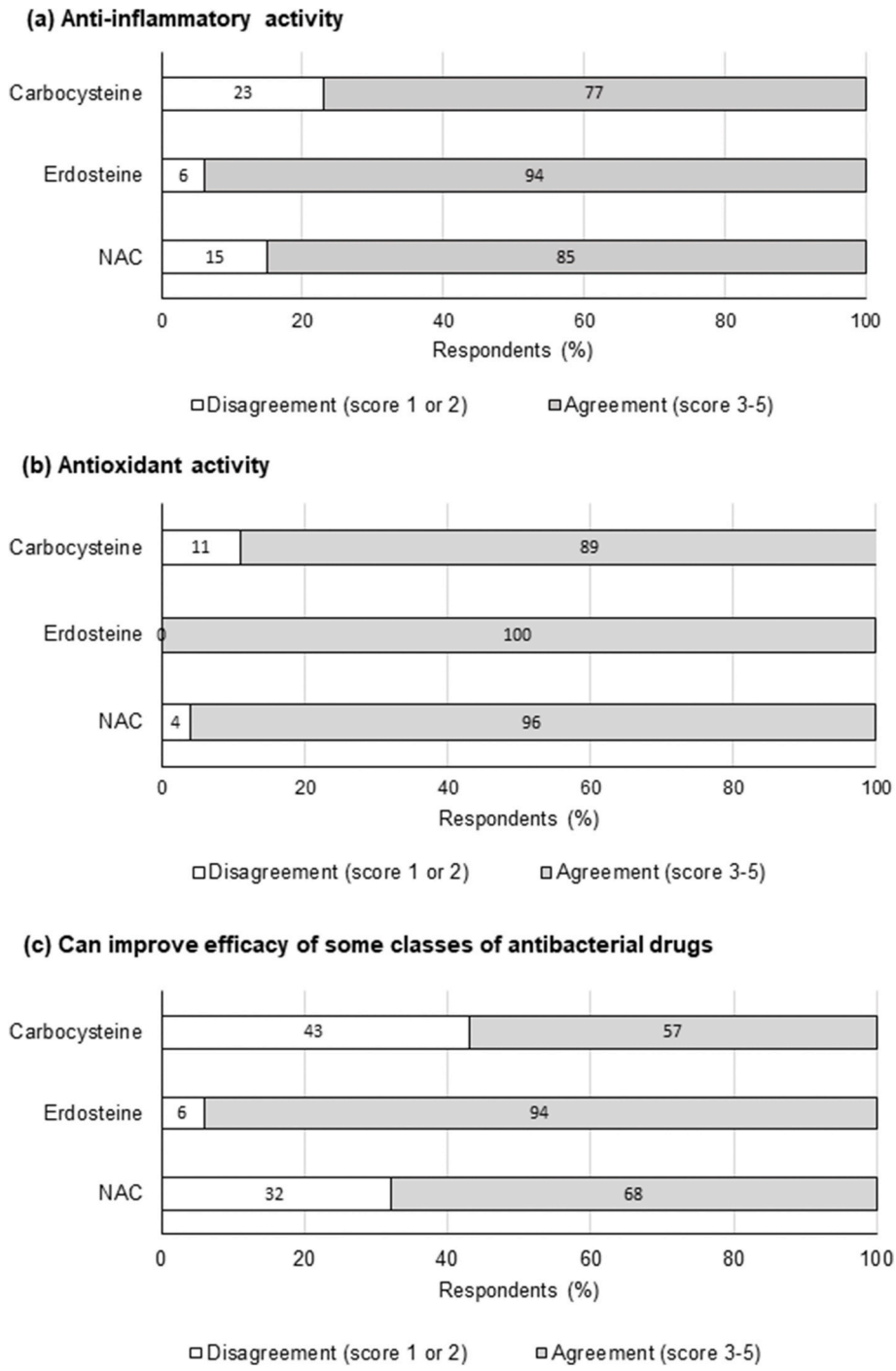

Fig. 3. Level of agreement for the mucolytic agents N-acetylcysteine (NAC), erdosteine and carbocysteine for Statement 2: Besides their efficacy on mucus rheology and production, mucolytic drugs exhibit other pharmacological properties of (a) anti-inflammatory activity, (b) antioxidant activity, and (c) can improve the efficacy of some classes of antibacterial drugs.

secretions of patients with acute bacterial exacerbations of chronic bronchitis [22]. Increased antibiotic concentrations in sputum were also seen in patients who received antibiotics in combination with erdosteine [23]. The reason for this discrepancy between expert opinion and published evidence is not known but may be influenced by their experience of using these mucolytic drugs in their patients. However, it highlights that these experts take into account the fundamental pharmacological differences between individual thiol-based mucolytic agents, which have been summarized in a recent review [17].

Although all three mucolytic agents have the potential to reduce the oxidative stress associated with COPD by reducing pro-oxidants and increasing antioxidants, each drug has a specific profile of activities [17]. All three mucolytic agents have also been shown to reduce the levels of reactive oxygen species (ROS) in COPD patients.

At present, it remains unclear whether the ability of these three thiol-based mucolytic agents to reduce the risk of acute exacerbations of COPD is related to their mucolytic, antioxidant, anti-inflammatory, or antimicrobial activities or, more likely, a combination of these properties.

There was consensus among the panel of experts that standard doses of mucolytics (erdosteine 94%, NAC 83%, carbocysteine 77%) are effective as short-term therapy for the treatment of symptoms of acute

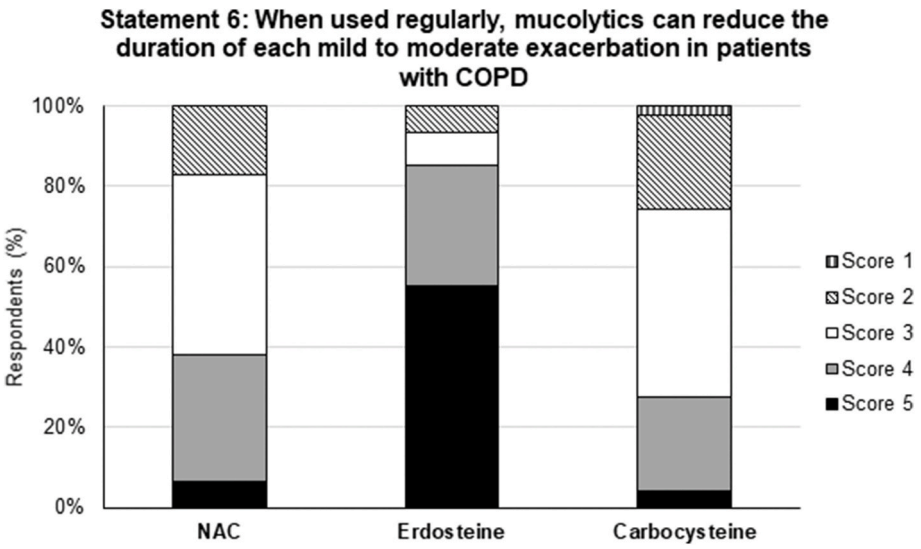

Fig. 4. Level of agreement for the mucolytic agents N-acetylcysteine (NAC), erdosteine and carbocysteine for Statement 6: when used regularly, mucolytics can reduce the duration of each mild-to-moderate exacerbation in patients with COPD. Number of respondents = 47. Score 1 = strongly disagree, 2 = disagree, 3 = agree, 4 = more than agree, and 5 = strongly agree.

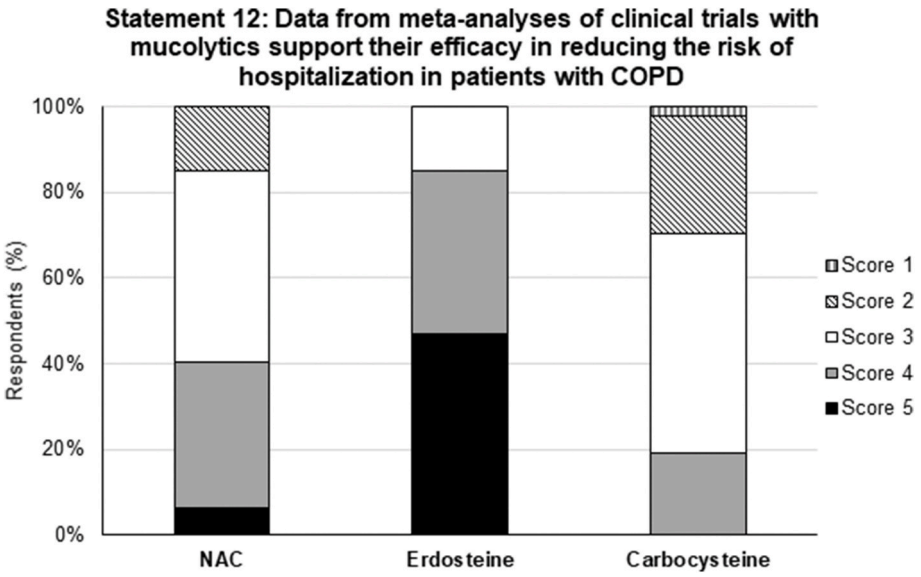

Fig. 5. Level of agreement for the mucolytic agents N-acetylcysteine (NAC), erdosteine and carbocysteine for Statement 12: Data from meta-analyses of clinical trials with mucolytics support their efficacy in reducing the risk of hospitalization in patients with COPD. Number of respondents = 47. Score 1 = strongly disagree, 2 = disagree, 3 = agree, 4 = more than agree, and 5 = strongly agree.

exacerbations of COPD when used in addition to other drugs.

Not surprisingly, the results showed a consensus that all three mucolytics have favorable side-effect profiles when used at approved doses and are associated with a high level of patient adherence. This is supported by a pooled analysis of studies on carbocysteine, erdosteine and NAC, which showed that adverse events were mild in severity and generally well tolerated by patients treated with any of the three agents [24].

Patients with COPD often have poor adherence to medication, for which there may be many contributing factors [25]. Their adherence is worse to inhaled versus oral medications [26]. Oral mucolytics may be particularly useful in people who have difficulties taking inhaled therapies and can be considered a safe and inexpensive therapy that contributes towards reducing exacerbations in patients with COPD.

At present, international guidelines recommend the use of mucolytics specifically in patients who are not receiving ICS [1]. This recommendation was based primarily on the results of the randomized, placebo-controlled BRONCUS study, which indicated that the possible benefit of standard doses of NAC (600 mg/day) in reducing exacerbations in patients with moderate-to-severe COPD may be limited to patients not treated with ICS [27]. This is in contrast with the PANTHEON study, conducted in Chinese patients with moderate-to-severe COPD, in which the treatment effect of NAC, administered at an approved high dose (1200 mg/day), was independent of the use of ICS [28].

In the PEACE study, the preventive effect of carbocysteine on exacerbations of COPD in Chinese patients was demonstrated only after adjusting for use of ICS, which were administered to a minority of the enrolled patients [29].

In the randomized, placebo-controlled RESTORE study, the use of erdosteine in moderate-to-severe COPD patients was associated with a reduction in the rate and duration of acute exacerbations of COPD irrespective of whether the patients were being treated with ICS [12,30].

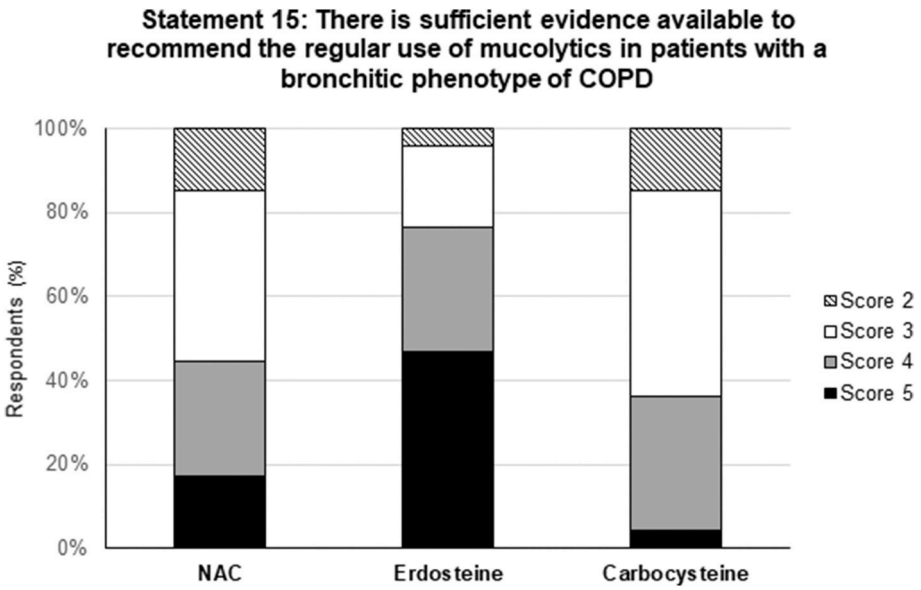

Fig. 6. Level of agreement for the mucolytic agents N-acetylcysteine (NAC), erdosteine and carbocysteine for Statement 15: There is sufficient evidence available to recommend the regular use of mucolytics in patients with a bronchitic phenotype of COPD. Number of respondents = 47. Score 1 = strongly disagree, 2 = disagree, 3 = agree, 4 = more than agree, and 5 = strongly agree.

There are findings that support the earlier use of mucolytic agents in patients with COPD with moderate airflow limitation, which accounts for a large proportion of COPD patients living in the community [12,13]. Earlier treatment of COPD that reduces the number, duration, or severity of exacerbation events may slow disease progression and improve patient health status [8].

Chronic bronchitis can be a clinical phenotype of COPD that is defined as chronic cough and sputum production for ≥3 months per year for two consecutive years [31]. Chronic bronchitis has been associated with a faster decline in lung function, increased risk of exacerbations, reduced health-related quality of life, and a higher mortality risk [31,32]. The results showed experts consensus that mucolytic agents are considered effective in the prevention of mild-to-moderate exacerbations and reduction of symptoms in patients with the bronchitis phenotype of COPD, findings consistent with a recent meta-analysis [33]. Also, there was consensus that sufficient evidence exists to recommend regular use of mucolytic agents in such patients. However, it remains unclear whether patients with a bronchitis phenotype of COPD benefit more from mucolytic therapy than patients with other phenotypes.

4.1. Strengths and limitations

Important strengths of the study include the Delphi study design and the size and quality of the panel of key international experts. Delphi studies typically have a sample size of 15–20 participants [34]. The results are enriched because the panel of 53 experts included clinicians and researchers from 12 different countries. The excellent response rate of 89% may partly be due to the online nature of the survey. The advantage of the Delphi technique is that it allows expert opinion to be gathered anonymously and consensus generated on specific topics, thereby supplementing the available evidence base for clinical decision-making.

There are some limitations of this study. First, the literature suggested to the panel was related only to the questionnaire topics and did not come from a systematic literature review. Second, the questionnaire was in English, which was not the native language of 11 of the 12 countries. However, as the panel are international experts, they were probably comfortable completing web-based questionnaires in English. Third, the panelists were mostly from European countries, which gives a geographical bias that may limit the ability to generalize these findings to all regions of the world.

5. Conclusions

The findings from this Delphi study involving a panel of key international experts suggest that wider use of mucolytic agents as add-on therapy for COPD is worth considering, especially in patients with less severe airflow obstruction, as the beneficial effects on exacerbations may contribute towards a slowing of disease progression. It is important to recognize that not all mucolytic agents are the same and their different mechanisms of action should be considered when deciding which mucolytic to use in an individual patient. These findings show some discrepancy between expert opinion and published clinical evidence and guidelines on mucolytics for the treatment of COPD, suggesting the need for new and/or updated large-scale clinical studies that would inform guideline revisions.

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CRediT authorship contribution statement

Alberto Papi: Conceptualization, Supervision, Writing - original draft. **Sergey Avdeev:** Investigation, Writing - review & editing. **Peter M.A. Calverley:** Investigation, Writing - review & editing. **Carlos R. Cordeiro:** Investigation, Writing - review & editing. **Milos Jesenak:** Investigation, Writing - review & editing. **Vladimir Koblížek:** Investigation, Writing - review & editing. **Diana Petkova:** Investigation, Writing - review & editing. **Paola Rogliani:** Investigation, Supervision, Writing - review & editing. **Hesham Tarraf:** Investigation, Writing - review & editing. **Nikolaos Tzanakis:** Investigation, Writing - review & editing. **Ruxandra Ulmeanu:** Investigation, Writing - review & editing. **Esra Uzaslan:** Investigation, Writing - review & editing. **Yochai Adir:** Investigation, Writing - review & editing.

Declaration of competing interest

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