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REVIEW

# Mucolytics/antioxidants: When Are They Useful?

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## ABSTRACT

Several national and international guidelines acknowledge the potential value of mucolytics/antioxidants N-acetylcysteine (NAC), carbocysteine and erdosteine, which are thiol-based drugs, in the treatment of stable chronic obstructive pulmonary disease (COPD). Thiols are also known to possess potentially important antioxidant and anti-inflammatory properties and exhibit antibacterial activity which may contribute to their effectiveness in treating patients with bronchitis or COPD. A careful evaluation of the results of pivotal randomized clinical trials and systematic reviews and meta-analyses supports the use of thiols in patients with stable COPD when added to standard maintenance therapy, but to date, there is no convincing evidence for their use to treat acute exacerbation of COPD. However, in the absence of head-to-head comparative studies, it is not easy to establish which thiol is preferable, although a consensus of international experts and data from a recent network meta-analysis suggest that the efficacy/safety profile of erdosteine is better than that of NAC and carbocysteine.

**Keywords:** Carbocysteine. COPD. Erdosteine. N-acetylcysteine (NAC). Thiols.

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## INTRODUCTION

In the 2023 version of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy for the treatment of COPD, it is suggested that the use of N-acetylcysteine (NAC) and carbocysteine reduces the risk of acute exacerbations of chronic obstructive pulmonary disease (AECOPD) and improves the quality of life in COPD patients who are not treated with an inhaled corticosteroid (ICS)[1]. In addition, the GOLD strategy also recommends that erdosteine may be used to prevent the onset of mild AECOPD regardless of concomitant use of ICS. However, it is stressed that it is still not clear which patient population may benefit most from taking thiols, due to the diversity of patients examined in clinical trials with these drugs and the possible effect of different concomitant therapies.

## THIOL-BASED MUCOLYTICS

NAC, carbocysteine, and erdosteine are three thiol-based drugs (thiols) that act as effective and safe mucolytic agents[2]. Thiols are classified as mucolytics because they reduce the elasticity and viscosity of bronchial secretions that have traditionally been approved for short-term use as treatments for chronic bronchitis[2]. However, it is now recognized that thiols can also differ in the way they act. The mucus structure is disrupted by NAC, a thiol containing a free sulfhydryl group (-SH). By giving electrons to the thiol groups of the mucin monomer cysteine (Cys) residues, it dissociates the disulfide bonds (S-S) that hold proteins together[3,4]. Due to this pharmacological effect, mucin oligomers depolymerize, mucin-rich secretions undergo rheological alterations, and the elasticity and viscosity of the mucus are subsequently reduced[5]. However, carbocysteine lacks a free SH group and, consequently, it does not break the S-S bonds. Instead, it likely substitutes fucomucins with sialomucins through intracellular sialyl transferase activity, regulates active ion transport across the airway epithelium, and improves mucociliary clearance velocity[6,7]. In contrast, there are two S atoms present in erdosteine, one in the aliphatic side chain as a thioether and the other in the heterocyclic ring (thiolactone)[8]. Erdosteine is a prodrug that is converted to the ring-opening molecule, metabolite M1, which has a pharmacologically active -SH group[8]. As a result, M1 exhibits many of the pharmacological effects attributed to erdosteine, including the mucolytic effect of this drug.

The therapeutic benefit of thiols is not limited to their mucolytic effect. Several preclinical studies and data collected from humans have shown the ability of these agents to interfere with inflammatory pathways[5,9,10], modulate human bronchial tone[11], reduce bacterial adhesion to the surface of respiratory epithelial cells[12-14], and inhibit biofilm formation or cause their rupture, thus improving the efficacy of antibiotic therapy[12]. However, not all of these additional actions have been documented for each of the three thiols[2]. The most important pharmacological action beyond mucolytic activity exerted by NAC, carbocysteine, and erdosteine is to influence oxidative stress[2].

## OXIDATIVE STRESS AND THIOLS

Oxidative stress is the overproduction of reactive oxygen species (ROS) such as superoxide ($O_2^{\bullet-}$),

hydroxyl radical (•OH), and hydrogen peroxide ($H_2O_2$), as well as reactive nitrogen species (RNS), relative to antioxidant levels, which in turn triggers the expression of inflammatory target proteins[2,15]. Oxidative stress is a significant factor in the pathophysiology of COPD[16]. In fact, the overproduction of inflammatory proteins may be a major contributor to the pathogenesis of COPD to the progression of this disease[2,15]. Glutathione (GSH) is an antioxidant found in cells that offers protection against several different oxidant species[16]. Therefore, the increased lung GSH levels observed in patients with COPD are an attempt to reduce excessive oxidant generation[16].

NAC prevents oxidative stress by acting as a direct ROS scavenger and altering the cellular redox state[17]. This could then affect the activation of transcription factor nuclear factor-κB and thus modify the inflammatory response. NAC acts as a precursor for the substrate (Cys) required in the biosynthesis of GSH[18]. Its role is to deliver -SH for utilization in biological processes and to provide a source for Cys. NAC increases GSH levels in plasma and bronchoalveolar lavage fluid and decreases the formation of ROS by alveolar macrophages and exhaled $H_2O_2$ in patients with COPD, which impacts on body redox balance[19,20].

Carbocysteine reacts with and reduces ROS, but its scavenger effects, which result from oxidation of its thioether group, are weaker than NAC[21]. Carbocysteine also exerts a direct action on neutrophils, reducing their chemotactic activity and their ability to adhere to endothelial cells[22]. Therefore, it would be able to reduce neutrophil activation and the release of cytokines and ROS[23]. In fact, carbocysteine antioxidant activity is closely related to cytoprotective and anti-inflammatory activities, as it reverses α1-antitrypsin inactivation and reduces the increased production of interleukin (IL)-8 due to increased intracellular •OH activity[24]. COPD patients treated with carbocysteine showed a marked reduction in exhaled 8-isoprostane[25].

By scavenging intracellular ROS, the erdosteine M1 metabolite blocks the effects of free radicals caused by cigarette smoke and controls the production of ROS by human neutrophils[26]. It decreases the formation of $O_2^{\bullet-}$, $H_2O_2$ and NO and the release of acid phosphatase and lysozyme from lipopolysaccharide-activated macrophages[8]. Experimentally, erdosteine stopped or reduced tissue damage caused by oxidative stress from various sources[27,28]. In COPD patients experiencing an acute exacerbation, erdosteine improved oxidant/antioxidant imbalance, and reduced exercise-induced oxidative stress and plasma levels of ROS and 8-isoprostane[29].

## THIOLS IN THE TREATMENT OF COPD

In addition to GOLD[1], several national and international guidelines and therapeutic strategies have acknowledged the potential value of mucolytics/antioxidants in the treatment of stable COPD based on the findings from randomized clinical trials (RCTs)[30-35].

### N-acetylcysteine

There have been a number of clinical trials with NAC in patients with COPD. The

Bronchitis Randomized on NAC Cost-Utility Study (BRONCUS)[36], the High-Dose N-Acetylcysteine in Stable COPD (HIACE)[37] and the Placebo-controlled study on efficAcy and safety of N-acetylcysTeine High dose in Exacerbations of chronic Obstructive pulmoNary disease [PANTHEON][38] were pivotal clinical trials that clarified the position of NAC in the treatment of COPD. In the first trial that involved 523 patients with COPD followed for three years, 600 mg of NAC daily was ineffective in preventing lung function deterioration and exacerbations in patients with COPD[36]. However, the subgroup analysis suggested that NAC could reduce the rate of AECOPD in patients not treated with ICS. The second study randomized 52 Chinese patients with stable COPD to NAC 600 mg twice daily and 56 to the placebo group[37]. Compared to placebo, NAC significantly decreased small airways resistance, as shown by improvements in forced expiratory flow between 25% and 75% ($FEF_{25\%-75\%}$) of forced vital capacity (FVC) and forced oscillation technique (FOT) and reduced the frequency of AECOPD. However, it did not significantly affect symptoms of COPD, exercise capacity, or quality of life parameters. The third trial, conducted in a Chinese population and enrolling 1006 patients with moderate to severe COPD, of whom 504 were treated with NAC and 502 with placebo in addition to their usual therapy, showed that the use of NAC 600 mg twice daily can prevent AECOPDs, especially in patients with COPD who had a significant smoking history and in those who did not receive ICS[39]. However, it should be noted that in the majority of countries where NAC is approved 600 mg twice daily is an off-label dosing regimen.

A meta-analysis that analyzed 13 studies including 4155 patients with COPD, 1933 treated with NAC, and 2222 with placebo or controls, revealed that NAC should be administered at a dose of at least 1,200 mg per day to patients with COPD who have an objective confirmation of airway obstruction to prevent AECOPDs, while patients with chronic bronchitis who do not have airway obstruction may benefit from regular treatment with 600 mg per day[40]. Furthermore, since the action of NAC at high doses is gradual and cumulative, regular therapy may be necessary for a prolonged period to avoid AECOPDs.

## Carbocysteine

There are several old studies with carbocysteine investigating the action of this drug in patients with COPD. Six hundred sixty-two outpatients with moderate to severe COPD participated in a prospective, double-blind, multicenter, six-month RCT in Italy[41]. Two hundred and twenty-three patients were randomly assigned to be treated with continuous treatment with carbocysteine (2.7 g once daily), 221 with intermittent 2.7 g of carbocysteine once daily (1-week courses alternated with 1-week intervals on placebo), and 218 to receive placebo. The baseline forced expiratory volume in the 1st second ($FEV_1$) did not differ significantly between groups. The results showed that the mean time to the first AECOPD was significantly prolonged (by 69 days in patients receiving continuous carbocysteine compared to placebo) and the mean number of days per patient experiencing acute respiratory illness was significantly decreased as compared to the group

receiving placebo and was associated with significantly lower antibiotic use during the trial period. The results of the evaluated endpoints did not differ substantially between the individuals allocated to intermittent therapy and those seen in the placebo group.

Seven hundred and nine individuals with moderate to severe COPD and a history of at least two AECOPDs during the previous two years were included in a randomized, double-blind, placebo-controlled, parallel-group, multicenter research in China[42]. For a year, 354 patients received 1500 mg of carbocysteine daily, while 355 received a placebo. The number of cumulative AECOPDs at one year was 325 in the carbocysteine group and 439 in the placebo group. However, only patients who had taken carbocysteine for six months or more had a reduction in AECOPDs. Carbocysteine also improved patient quality of life but did not induce a significant increase in lung function compared to placebo after one year of treatment.

Observational studies have also showed that a reduction in the rate of AECOPDs at one year was completely independent of the use of ICSs[43,44].

A meta-analysis that included data from four studies involving 1,357 patients has evaluated the long-term use of carbocysteine[45]. The findings suggested that long-term use of carbocysteine (500 mg three times a day) may be associated with lower AECOPD rates, fewer patients with at least one AECOPD, and better quality of life. However, the authors of this meta-analysis pointed out that these conclusions should be used with caution, as they found a possible publication bias that could lead to over-estimated results.

## Erdosteine

A comprehensive review and meta-analysis published in 2010 demonstrated the efficacy of erdosteine in people with stable or worsened chronic bronchitis/COPD[46]. Fifteen RCTs with 1,046 adult patients were included in the meta-analysis. Only one of these studies had been published after 1996, and unpublished data supplied by manufacturers were also used. Compared to placebo and other mucolytics, erdosteine treatment was associated with a substantial advantage in symptom reduction. Furthermore, erdosteine plus antibiotics were more effective than antibiotic monotherapy in patients with chronic bronchitis/COPD, particularly to treat exacerbations induced by acute infections. However, the benefit of erdosteine on cough and sputum scores was less significant, due to the short duration of therapy in the reviewed RCTs.

The landmark study Reducing Exacerbations and Symptoms by Treatment with ORal Erdosteine in COPD (RESTORE) was published in 2017[47]. Four hundred and sixty-seven COPD patients who had suffered two or more AECOPD requiring medical treatment in the 12 months prior to enrolment, but no AECOPD in the previous two months, were recruited. In addition to their regular maintenance medications for COPD, 228 patients received oral erdosteine at the recommended dose of 300 mg twice daily for one year after a two-week run-in phase. In comparison, 239 patients received placebo treatment

for 12 months. The rate of mild AECOPDs was affected by erdosteine (0.23 versus 0.54 AECOPD/patient/year for erdosteine and placebo, respectively), which resulted in a 19.4% decrease in the rate of AECOPDs. Interestingly, the AECOPD rate was 0.93 compared to 1.16 (–19.5%) in ICS users and 0.89 versus 1.10 (–19.3%) in ICS non-users. No significant differences were found in terms of the frequency of moderate and severe AECOPDs. Regardless of the severity of the episode, erdosteine reduced the duration of all AECOPDs by 24.6% (9.5 days with erdosteine versus 12.6 days with placebo). In addition, it was also able to significantly reduce subjective disease severity scores rated by the patient and the physician and minimize the need for relief medication.

There was a 47% reduction in the mean rate of AECOPDs (0.27 versus 0.51 AECOPD/patient/year, respectively) and a 58.3% reduction in the rate of mild AECOPDs (0.23 versus 0.53 mild AECOPD/patient/year) with erdosteine compared to placebo in the 254 RESTORE patients with post-bronchodilator $FEV_1$ between 50 and 79% predicted, of which 126 received erdosteine and 128 placebo[48]. The mean duration of mild and moderate to severe AECOPDs was significantly reduced in erdosteine-treated patients (9.1 versus 12.3 days for placebo). Furthermore, erdosteine increased both the mean time to first AECOPD (182 days versus 169 days for placebo) and the mean time without AECOPDs (279 days with erdosteine versus 228 days with placebo). The number of eosinophils in the blood did not affect the response to treatment. Using an ICS in addition to erdosteine had no impact on the frequency and duration of AECOPDs, and the time to first AECOPD in patients with moderate COPD. Forty-three of 126 erdosteine-treated patients worsened (7 moderate to severe AECOPDs), compared to 62 of 128 placebo-treated patients (14 moderate to severe AECOPDs)[49]. Patients treated with erdosteine had a significantly shorter mean duration of corticosteroid treatment (on average 11.4 days versus 13.3 days for placebo). Moreover, the number of patients who required antimicrobial treatment with/without oral corticosteroids was significantly lower among those treated with erdosteine (71.4% versus 85.8% of those treated with placebo). Regardless of the intensity of AECOPD, patients treated with erdosteine exhibited substantial improvements from baseline in the total scores of the St. George's Respiratory Questionnaire and subjective severity scores of the disease rated by the patient and the physician compared to placebo-treated patients. There were no significant differences between erdosteine and placebo in any of these measures among patients with post-bronchodilator $FEV_1$ between 30 and 49% predicted[49].

According to a new meta-analysis that included relevant studies published up to 31 July 2017, but that excluded unpublished data provided by manufacturers as they can make it difficult to assess potential bias[50], erdosteine improves quality of life, reduces respiratory symptoms, and maintains lung function[51]. Furthermore, it has been shown that it can reduce the overall risk of chronic bronchitis/COPD exacerbations and that of experiencing at least one exacerbation, lengthen the time until the first exacerbation, shorten the duration of exacerbations, and reduce the risk of hospitalization from COPD.

## META-ANALYSIS PERFORMED TO CLARIFY THE ROLE OF MUCOLYTICS IN THE TREATMENT OF PATIENTS WITH STABLE CHRONIC BRONCHITIS/COPD

According to a pairwise and network meta-analysis, mucolytics are beneficial in preventing AECOPDs when taken as additional therapy in individuals who are frequent exacerbators[52]. Furthermore, they were effective regardless of the degree of airway obstruction or in the case of erdosteine, the concomitant use of ICSs. Specific variations in the research designs and factors related to the patient, such as AECOPD history and ethnicity, were possible impact modifiers for the statistical models used, although neither respiratory function nor corticosteroid usage altered the analyses.

Due to the lack of head-to-head comparisons between different mucolytic/antioxidant agents in RCTs to directly compare the efficacy profile of high-dose NAC (1200 mg/day), carbocysteine (1500 mg/day) and erdosteine (600 mg/day), a pairwise and network meta-analysis of the available data was conducted to compare the actual efficacy of these three thiols on AECOPD. NAC, carbocysteine, and erdosteine significantly decreased the incidence of AECOPD[53]. However, when the probability that each intervention arm was the most effective was calculated by counting the proportion of iterations in the chain in which each intervention arm had the highest mean difference and, then, the degree of effectiveness was determined by the area under the cumulative classification curve (SUCRA), which is the summary of these probabilities, the SUCRA analysis favored erdosteine. The number of patients needed to treat (NNT) with erdosteine for one year to avoid one AECOPD compared to placebo was 10.11. At the same time, the NNTs with carbocysteine (30.92) and NAC (15.69) were not substantially different from placebo. Erdosteine and NAC considerably reduced the duration of AECOPD. However, only erdosteine reduced the chance of hospitalization due to AECOPD.

A second meta-analysis was carried out by the Cochrane Airways Group[54]. It included a variety of mucolytics in addition to NAC, carbocysteine, and erdosteine, with a search for articles published by April 2019. Thirty-eight studies were selected, with a total of 10,377 participants recruited. This extensive meta-analysis indicated that mucolytics can cause a small reduction in the incidence of AECOPDs in people with chronic bronchitis or COPD while not appearing to increase side effects. If everyone takes the medication every day for an average of nine months, one in every eight patients can avoid experiencing AECOPD. Mucolytics are associated with a decrease in monthly disability days and a decrease in hospital admissions. However, there is no evidence that they significantly decrease lung function deterioration, and it is uncertain if they enhance quality of life. Furthermore, the data are too inconsistent to determine whether there is an influence on mortality. Given all this, the authors believed that mucolytics could be used as a treatment option for patients with frequent AECOPDs who cannot take other therapies, such as ICSs or long-acting bronchodilators or as an adjunctive treatment in addition to other therapies to reduce AECOPDs because this appears to be the main potential benefit, particularly

with erdosteine in reducing mild to moderate exacerbations, i.e., earlier in the disease.

## THIOLS IN THE TREATMENT OF AECOPD

Both the European Respiratory Society/American Thoracic Society have published guidelines on the management of AECOPDs[55], that along with a recent European consensus on the standardization of management of hospitalized AECOPD[56] and the 2023 GOLD document[1], do not mention the use of mucolytics/antioxidants in the treatment of AECOPD. However, some RCTs and systematic reviews and meta-analyses have explored the use of mucolytics in this setting.

When administered for 7 to 30 days, NAC was not associated with any significant efficacy in outpatients with mild[57] or in hospitalized patients with moderate to severe exacerbations of their COPD[58-60]. On the contrary, at two months of follow-up (but not at one month of follow-up), erdosteine was associated with fewer recurrent AECOPDs and symptoms (measured by the Breathlessness, Cough, and Sputum Scale) and a higher $FEV_1$% predicted at the end of treatment (but not at two months of follow-up)[61].

Several systematic reviews and meta-analyses have been conducted to obtain a more complete view of the impact of thiols on the treatment of AECOPD. The analysis carried out to verify whether NAC can promote the improvement of clinical symptoms and lung function in patients with AECOPD identified 15 studies, of which 12 were retrospective analyses and three were RCTs[62]. In total, 1,605 patients were included. The results concluded that NAC could promote symptom improvement and faster resolution of exacerbations in patients with AECOPD, improve lung function in $FEV_1$ and $FEV_1$/FVC, and improve antioxidant capacity. However, the studies that were included in this meta-analysis were small.

Data obtained from six RCTs with a total of 369 patients affected by AECOPD showed that the addition of erdosteine (600 to 900 mg/day) for up to seven days to standard AECOPD therapy results in faster improvement in clinical symptoms and spirometric data[62]. For example, the intensity of dyspnea decreased by –77.7% in the presence of erdosteine versus –63.6% in its absence, the frequency of cough, on the other hand, decreased by –65.4% versus –44%, the difficulty of expectoration by –68.9% versus-50% and the viscosity of sputum by –68% versus –38.4, while $FEV_1$ increased +19% versus +4.8%.

Twenty-one appropriate RCTs with 1,411 patients with moderate or severe AECOPDs were found after a thorough review and meta-analysis. In addition to studies with NAC and erdosteine, other investigations using ambroxol, bromhexine, and hypertonic saline were also included in the analysis[64]. Evidence supported a moderate confidence level that mucolytics reduced symptoms with a reasonable treatment success rate in AECOPDs compared to control. However, while mucolytics may have helped cough and expectoration efficiency, they did not appear to impact dyspnea significantly. In addition, mucolytics were associated with a negligible positive effect on arterial blood oxygen partial pressure and oxygen saturation.

Nevertheless, a clinical practice guideline for the pharmacological management of AECOPD from the American Academy of Family Physicians states that there is insufficient evidence to support the role of mucolytics in the treatment of AECOPD[65]. In fact, there is no difference between treatments with and without mucolytics or placebo when dyspnea is the outcome and the evidence for the reduction of the number of AECOPDs at one month is poor and becomes insufficient to claim significant benefit at three months.

## ARE MUCOLYTICS/ANTIOXIDANTS USEFUL IN THE TREATMENT OF COPD?

Although today, COPD guidelines and recommendations recognize the efficacy of thiols in the treatment of COPD[1,30-35], basic information on their correct positioning in the therapeutic approach to COPD is still lacking.

However, a careful evaluation of pivotal RCTs and systematic reviews and meta-analyses supports the use of thiols in patients with stable COPD when added to the usual maintenance therapy for COPD, as recommended by the latest GOLD document[1], while there is no clear-cut benefit in using thiols to treat AECOPDs. The question remains as to whether the benefit of these mucolytic/antioxidant agents is only in preventing the occurrence of mild AECOPDs or whether they can also be applied to moderate and severe AECOPDs.

The severity of AECOPDs is usually classified a posteriori, according to the drugs used to control the symptoms and where they were administered (outside the hospital or while hospitalized)[1]. However, such an approach in the classification of AECOPDs introduces great variability and bias. Indeed, different hospitals, clinicians, or patients – especially in different continents and cultures – may have individual preferences or habits that influence decisions on the type of treatment to be chosen and where it should be administered.

It is, therefore, no surprise that recently the Lancet Commission suggested considering only severe or non-severe exacerbations, eliminating the categories of mild or moderate exacerbations[66]. However, given the evidence that patients with mild to moderate exacerbations may be missed in general practice, despite the recognition that the fastest lung function decline occurs early in the disease, this conclusion is somewhat controversial. The use of a drug class earlier in the disease that is inexpensive, orally active and safe is surely what should be encouraged to prevent patients from needing treatment later in the disease when they have moderate to severe exacerbations.

The use of accessory respiratory muscles or paradoxical movements of the chest wall, or both, clinically significant hypoxemia, new or worsening hypercapnia or respiratory acidosis, decreased vigilance (such as confusion, lethargy or coma), and failure to respond to initial medical treatment are classification criteria for severe exacerbations. Other factors include right heart failure, cardiac ischemia, hemodynamic instability, or clinically significant arrhythmia. It would be interesting if data from pivotal trials were re-evaluated based on this type of classification of the severity of AECOPDs. It would not be surprising if the conclusions of such a reevaluation

could generate a different recommendation from the one in the GOLD document[1].

In any case, it is crucial to consider the point of view of those who regularly treat COPD patients in everyday practice. Ninety-eight % of participants in a recent Delphi study that gathered the opinions of a panel of international COPD experts from 12 different countries on a variety of topics related to the use of mucolytics in the treatment of COPD believed that standard doses of these agents were useful in the treatment of chronic bronchitis and COPD[67]. The consensus among these specialists was that consistent use of these mucolytic medications successfully reduced the incidence and duration of AECOPDs. Regular use of mucolytics can also lengthen symptom-free periods and the interval between AECOPDs. These views agree with the GOLD recommendations[1]. However, in contrast to the GOLD advice, experts also agree that mucolytics are useful in avoiding mild to moderate exacerbations, not only mild ones.

In the absence of head-to-head comparative studies, however, it is difficult to determine which thiol is preferred and ideally in which patient group they would benefit most. Nonetheless, the consensus was consistently higher for erdosteine among the experts who participated in the Delphi study mentioned above[66]. This supports data from a recent network meta-analysis in which the overall efficacy/safety profile of erdosteine was superior to that of NAC and carbocysteine[53]. However, the choice of thiol to be used also depends on its presence in the country where the patient with COPD is to be treated and taking into consideration dose, as most of the benefit with NAC has been observed with high dose (unapproved) regimes.

A further possible use of thiols in COPD, which unfortunately has not yet been evaluated by a specifically designed RCT, is to add them when withdrawing ICS from triple therapy that also includes a long-acting $\beta_2$-agonist (LABA) and a long-acting muscarinic antagonist (LAMA) in patients with stable COPD, at least in those with moderate COPD defined by spirometry[48]. Since a risk of AECOPD is still present when ICS is discontinued[68], even if dual bronchodilation with LABA and LAMA proves effective in reducing this risk in many patients with COPD[69], the addition of a thiol at appropriate doses instead of ICS could help increase the chance of preventing exacerbations[70]. The documentation that thiols effectively reduce the risk of AECOPDs in the absence of an ICS[39,43,44,47,48] reinforces this therapeutic hypothesis.

Obviously, there is a need to identify the patient population that may benefit from taking thiols. Experts believe that in the presence of chronic bronchitis, which must be understood as a clinical phenotype of COPD, mucolytic agents are effective in preventing mild to moderate AECOPD and reducing symptoms[67]. This view is supported by the results of a recent meta-analysis[54]. It is yet unknown, nevertheless, whether mucolytic treatment is more effective for COPD patients with the bronchitis phenotype than for COPD patients with other phenotypes[67].

Unless complemented by thickening of the bronchial wall, a characteristic of chronic bronchitis, the emphysema-hyperinflation phenotype is less likely to develop AECOPDs[71]. In this phenotype, the use of dual bronchodilator therapy improves inspiratory capacity, symptoms, and quality of life and reduces

dynamic lung hyperinflation and the need for rescue medication[69]. Thiols could be added to prevent the occurrence of exacerbations, also because there is documentation that at least NAC exerts beneficial effects on air trapping[37]. NAC enhances the bronchodilator effects of muscarinic receptor antagonists, but not those of $\beta_2$-agonists[72]. On the other hand, erdosteine improves the airway response to salbutamol in patients with mild to moderate COPD due to its protection against lipid peroxidation rather than its scavenging function, because $\beta_2$-adrenoceptor lipid peroxidation is not reversed by NAC administration[8]. However, it must still be established whether the level of bronchial obstruction may influence the effects caused by thiols. Furthermore, it is necessary to discriminate the effect of thiols at the level of the middle bronchi and small airways, as their impact against AECOPD may be related to their mucolytic activity and anti-inflammatory effect at the level of the distal airways, resulting in a reduction in pulmonary hyperinflation[5]. Nonetheless, it is time to reconsider the wider use of thiols in the prevention of exacerbations of COPD.

## DISCLOSURES

M.C., and C.P. are or have been consultants to Zambon (Italy), a company that manufactures and markets NAC, and to Edmond Pharma (Italy), a company that manufactures and markets erdosteine. P. R. participated as a lecturer in scientific meetings sponsored by Edmond Pharma and Zambon. Her department was funded by Zambon. M.G.M. has received a research grant partially funded by Zambon (Italy).

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