

# Mucoactive and antioxidant medicines for COPD: consensus of a group of Chinese pulmonary physicians

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**Abstract:** Airway mucus hypersecretion is a frequent symptom associated with acute and chronic airway disease. Inhibition of mucus production or promotion of mucolysis not only relieved symptoms but also improved disease outcomes. There are numerous available mucoactive medicines for prescription, and how to select them properly for different diseases is important for clinical practice. So far, there is no one consensus or guideline reported. A group of Chinese pulmonary physicians worked together to complete this consensus based on literature review, summarized mechanism and usage of each classical mucoactive medicine. In general, antioxidant mucoactive medicines play an important role in chronic airway disease, including but not limited to airway mucus clearance, reduced acute exacerbation and improved pulmonary function.

**Keywords:** sputum, chronic bronchitis, mucolysis

## Introduction

COPD is defined as persistent air flow limitation with continuous progression. But it is a treatable and preventable disease. A survey among 20,245 adults in 7 areas of the People's Republic of China showed that the prevalence of COPD in the population aged older than 40 years was 8.2%.<sup>1</sup> Global disease burden report indicated that COPD would rank as the fourth disease in the People's Republic of China in 2013.<sup>2</sup> Most importantly, acute exacerbation of COPD (AECOPD) accelerates pulmonary function decline, reduces quality of life and increases medical cost. Risk factors analysis suggested that patients who have acute exacerbations more than 3 times carried 4 times higher mortality and morbidity compared to those who do not have acute exacerbations.<sup>3</sup> Therefore, the prevention of acute exacerbation is an important strategy to reduce lung function decline, improve quality of life and eventually reduce COPD mortality.<sup>4</sup>

COPD is a heterogeneous disease based on clinical presentation, genetic background, pathophysiology and therapeutic response. There is no doubt that precision medicine is required to treat COPD, considering its versatile and complicated profile. Cilium-beating dysfunction, mucus hypersecretion, bacteria colonization, airway inflammation and oxidative stress contribute to COPD pathogenesis, while identification of the gene susceptible to occupational exposure and smoke may reveal intrinsic factors. Thus, COPD prevention, diagnosis and treatments should be a long-term, comprehensive, persistent and individualized program. In the past 10 years, results from several randomized controlled trials (RCTs) have increased the understanding of the role of expectorant/antioxidant therapy in COPD. These results have also been

cited in the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, with contribution from Chinese scholars.<sup>5,6</sup>

Considering that there is no guideline or consensus on COPD expectorant/antioxidant therapy, the editorial office of the *International Respiratory Journal* brought together specialists in the field to draft this consensus in order to guide clinical use of expectorant/antioxidant medicine in COPD.

## Methodology

The PubMed, Chinese Biology Abstract, Chinese Academic Journal database and WanFang database were used to identify relevant articles published from 2005 to 2016. The initial literature search identified 316 published articles, of which there were 80 potentially relevant references (41 from English and 39 from Chinese literatures). Finally, 76 references were eligible for this review after group discussion, and eventually 66 references were included in this review. Disagreements were resolved by consensus.

## Importance of mucoactive therapy

Cough and phlegm are the main clinical presentations, as well as key criteria, for COPD phenotype classification. Airway mucus hypersecretion is one of the insulting factors for airflow limitation, lung function decline and COPD acute exacerbation.<sup>7</sup> Several studies have shown that persistent cough with sputum is correlated with the decline of forced expiratory volume in one second (FEV<sub>1</sub>), hospitalization and mortality,<sup>8,9</sup> while mucoactive therapy could relieve small airway obstruction, reduce bacteria colonization and acute exacerbation, and improve health-related quality of life. A study conducted by Vestbo et al<sup>10</sup> showed that chronic airway mucus hypersecretion is correlated with FEV<sub>1</sub> decline, especially in male patients, with additional 22.8 mL decrease each year. Khurana et al<sup>9</sup> showed evidence that sputum neutrophil and eosinophil counts, eotaxin-1, monocyte chemoattractant protein (MCP)-1, tumor necrosis factor (TNF)- $\alpha$  and interleukin (IL)-6 levels in sputum supernatant in persistent-expectoration COPD patients was higher than the levels in patients who do not have cough and sputum secretion. It indicated that mucoactive therapy may relieve airway inflammation and expectoration symptoms.<sup>11</sup> Other studies showed that COPD patients with and without long-term cough and sputum had acute exacerbation at the rate of 2.2/patient-year and 0.97/patient-year; 1.8/patient-year and 0.66/patient-years for moderate exacerbation; 0.43/patient-year and 0.22/patient-year for hospitalization, respectively. The proportions of acute exacerbation were

55% and 22% individually.<sup>12</sup> These results strongly indicated the necessity of mucoactive therapy in COPD.

## Importance of antioxidant therapy

Oxidative stress is one of the key contributors to COPD pathogenesis, due to the imbalance of oxidant and antioxidant systems, which leads to the accumulation of reactive oxygen species (ROS), resulting in organ tissue injury. Multiple cells are involved in the pathogenesis of COPD, including neutrophils, eosinophils, macrophages, lymphocytes, as well as the airway epithelial cells etc. The activation of these cells results in persistent and chronic inflammation, as well as the imbalance of oxidant/antioxidant status. Smoking and air pollution are two major risk factors for COPD. Smoking could increase ROS production. When antioxidants cannot metabolize ROS, the cell membrane, proteins, glycosides and DNA of the airway epithelium are damaged due to chronic inflammation.<sup>13</sup> Moreover, the endogenous source of oxidative stress is the inflammatory cells such as macrophages, neutrophils and eosinophils. These cells release large amounts of ROS after smoking exposure. Although antioxidants could scavenge free radicals, quantities of ROS would be accumulated when the antioxidants are exhausted.<sup>14</sup> The compound 8-isoprostane, a biomarker of oxidation, increased in expiration condensation fluid obtained from COPD patients and smokers;<sup>15,16</sup> moreover, this also correlated positively with the degree of emphysema and modified Medical Research Council (mMRC) dyspnea score, while being negatively correlated with partial pressure of arterial oxygen PaO<sub>2</sub>, diffusing capacity of the lungs for carbon monoxide (DLCO), 6 min walk test and maximum exercise work load.<sup>17,18</sup>

## Mucoactive and antioxidant drugs

There are many mucoactive medicines, such as mucolytics, mucokinetic agents, mucoregulators and expectorants. Not all mucoactive medicines have both expectorant and antioxidant properties. Herein, we summarized 4 of them that have been frequently used in clinical practice with evidence of literature support, such as N-acetylcysteine (NAC), carbocysteine, erdosteine and ambroxol. They also are routinely prescribed drugs for COPD (Table 1).

### N-acetylcysteine

NAC has been used in clinical practice since the 1960s. It contains one free thiol and it breaks down the disulfide bond, depolymerizes the oligomer accumulation of mucin and then reduces sputum viscosity.<sup>19</sup> The overall functions of NAC are described as follows.<sup>20</sup>

**Table 1** Summary of mucoactive medicines

Name	Classification	Major function	Antioxidant properties
NAC	Mucolytic agent	Breaks disulfide bonds	Yes
Ambroxol	Mucokinetic drug	Stimulates surfactant production	Yes
Carbocysteine	Mucoregulator	Antioxidant and anti-inflammatory activity, modulates mucus production	Yes
Erdosteine	Mucolytic agent	Modulates mucus production	Yes

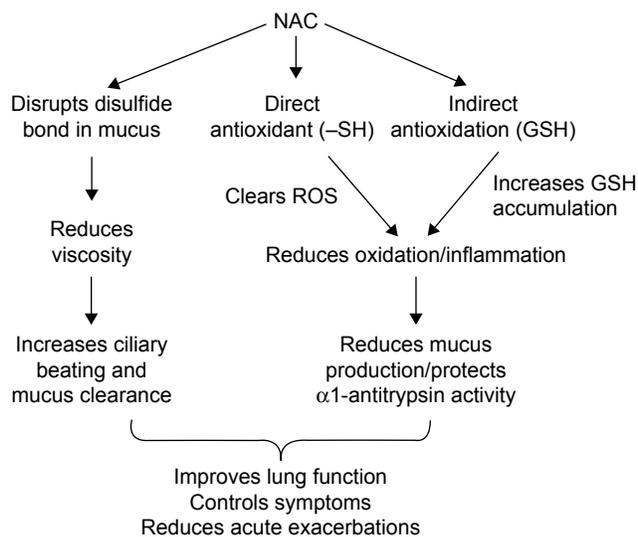
**Abbreviation:** NAC, N-acetylcysteine.

### Mucolytic activity

NAC breaks down the disulfide bond in mucin glycopeptides to reduce sputum viscosity and makes expectoration easy. NAC can also lyse sputum DNA, increase airway surface liquid thickness and promote airway clearance. It also inhibits mucus secretion and cell hyperplasia, as well as increasing MUC5AC expression.<sup>21</sup> In addition, it increases beating of cilia, stimulates gastric–lung vagus reflexion to improve expectoration.<sup>22</sup>

### Antioxidant property

NAC has direct and indirect antioxidant properties (Figure 1). The direct function includes the binding of the thiol group to free radicals, hydrogen peroxide and hypochlorite to clear ROS.<sup>23</sup> It also binds to glutathione peroxidase to reduce production of lipid peroxide. The indirect functions include



**Figure 1** Mechanism of NAC pharmacology in COPD patients.

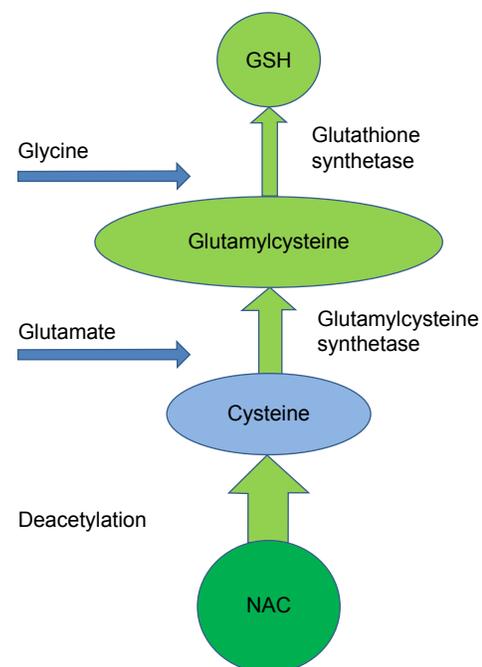
**Notes:** NAC can directly break disulfide bonds in mucus to decrease mucus viscosity, thus improving ciliary beating and mucus clearance. NAC clears ROS through –SH binding, possessing antioxidant properties, as well as having the indirect function of facilitating GSH accumulation. The decrease of ROS and increase of GSH reduce airway inflammation and airway mucus production. All these contribute to improved lung function and reduced acute exacerbation.

**Abbreviations:** –SH, thiol; GSH, glutathione; NAC, N-acetylcysteine; ROS, reactive oxygen species.

synthesis of glutathione and maintenance of adequate levels of glutathione to prevent cell damage (Figure 2). Oral intake of 600 mg/d NAC for 5 d can significantly increase bronchoalveolar lavage fluid (BALF) glutathione levels, indicating that NAC plays an important role in indirect antioxidantation.

### Inhibition of lung inflammation

Oral intake of NAC can decrease the H<sub>2</sub>O<sub>2</sub> level in expiration air and reduce NF-κB-mediated lung inflammation.<sup>24</sup> Signal transduction in redox-sensitive cells is also inhibited by NAC to reduce endothelial injury, improve imbalance of oxidant-antioxidant and further prevent airway injury.<sup>25</sup> The thiol group in NAC reduces the activity of elastase, decreases



**Figure 2** The synthesis of GSH from NAC and its metabolites.

**Notes:** NAC is transferred to cysteine after deacetylation. Cysteine reacts with glutamate to become glutamylcysteine under the action of glutamylcysteine synthetase; then, glutamylcysteine and glycine yield GSH in the presence of glutathione synthetase.

**Abbreviations:** GSH, glutathione; NAC, N-acetylcysteine.

plasma myeloperoxidase (MPO) and the capacity of elastic protease, as well as decreasing the production of lactoferrin and eosinophil cationic protein in BALF, neutrophil chemoattractant activity<sup>26</sup> and neutrophil chemoattractant release in sputum of COPD patients.<sup>27</sup> It also attenuates the lung injury induced by oxidative stress, lung inflammation and airway remodeling.

#### Decreases microbial pathogenicity

NAC could reduce the adhesion of *Haemophilus influenzae* and *Streptococcus pneumoniae* to epithelia of oropharynx, inhibit bacteria colonization and growth, improve the anti-infective ability, and decrease the frequency of acute exacerbation.<sup>28</sup> NAC also could inhibit virus replication and reduce virus titer through decreasing cell cytosol H<sub>2</sub>O<sub>2</sub> and restore cell sulfhydryl levels.<sup>29</sup> By inhibiting expression of adhesion molecules after respiratory syncytial virus infection, NAC could adjust cytosol H<sub>2</sub>O<sub>2</sub> level to restore glutathione for epithelium protection.<sup>30</sup>

## Carbocysteine

### Mucoregulator

Carbocysteine is the thiol derivative of L-cysteine with free radical-scavenging and anti-inflammatory properties.<sup>31</sup> Carbocysteine stimulates the production of low-viscosity sialomucin and decreases the production of high-viscosity mucin to improve sputum clearance. It also binds to the disulfide bond through the carboxymethyl group to improve sputum elasticity and viscosity to increase ciliary clearance.<sup>32</sup>

### Anti-inflammatory and antioxidant properties

Carbocysteine is a strong scavenger of hypochlorite and free radicals. It can significantly inhibit IL-8 production from peripheral neutrophils.<sup>33</sup> It also inhibits conversion of xanthine dehydrogenase to xanthine oxidase to exert anti-inflammatory effects.<sup>34,35</sup>

### Anti-infective activity

Carbocysteine reduces bacterial colonization by decreasing the expression of adhesion molecule-1, especially for *Streptococcus pneumoniae*.<sup>36</sup>

## Erdosteine

Erdosteine is an antioxidant and mucoactive medicine containing thiol group. It has the following activities.

### Viscosity regulation

Three free thiol metabolites are produced after oral intake, and these thiol metabolites break the disulfide bond to change

sputum viscosity and promote airway clearance while retaining the antitussive effects.

### Anti-inflammatory and antioxidant activity

Erdosteine scavenges free radicals and protects  $\alpha$ 1-antitrypsin activity<sup>37</sup> to exert its anti-inflammation and antioxidant properties.

### Anti-infective activity

Erdosteine metabolites significantly increase secretory immunoglobulin A (sIgA)/albumin and lactoferrin/albumin ratios, as well as improving antibiotic penetration in airway mucosa, thus reducing bacterial adhesion.<sup>38,39</sup>

## Ambroxol

Similar to NAC, ambroxol regulates mucus secretion and exerts anti-inflammatory effect at large doses. The main mechanisms are described as follows.

### Viscosity regulation

Ambroxol stimulates serous secretion and increases airway surface liquid depth, in addition to thinning of the thick mucus and sputum. It also promotes surfactant production, increases ciliary beating and promotes expectoration.<sup>40,41</sup>

### Anti-inflammatory and antioxidant effects

Ambroxol has high affinity to lung tissue; it has anti-inflammatory and antioxidant properties. Through promotion of surfactant production, the surface tension of alveoli could be reduced, thereby preventing alveolar trap and decreasing alveolar and airway pressure. By free radical clearance and inhibition of leukotriene and histamine production, ambroxol effectively attenuates inflammation from macrophages and neutrophils. It also activates the cytosolic glutathione system to promote glutathione production to clear hyperoxidates, leading to reduced airway responsiveness and reactivity.<sup>42</sup>

### Antibacterial effects

Combination of antibiotics and ambroxol could increase antibiotic concentration in the lung tissue and improve bacterial clearance and lung infection, while reducing antibiotic use.<sup>43</sup>

## Clinical studies of mucoactive/antioxidant drugs on COPD

### Mucoactive/antioxidant drugs could decrease acute exacerbation

Several RCT studies have shown that mucoactive/antioxidant medicines could significantly decrease acute exacerbation in

COPD. Pela et al<sup>44</sup> reported, for the first time, on the effects of NAC in stable COPD patients and found that NAC reduced acute exacerbation in 169 moderate-to-severe COPD patients. The patients enrolled in that study were assigned randomly to control standardized treatment group and standardized treatment with NAC group with a dose of 600 mg/d. After 6 months, the overall exacerbation in the NAC group decreased 41%. In 2005, 523 patients were enrolled and followed for 3 years in the Bronchitis Randomized on NAC Cost-Utility Study (BRONCUS) study;<sup>45</sup> the results showed that NAC (600 mg/d) did not show any difference on acute exacerbation. However, for those who did not use inhaled corticosteroids (ICSs), acute exacerbation rate dropped 21% ( $P < 0.05$ ). The HIACE<sup>46</sup> study, conducted in Hong Kong in 2013, showed that treatment with NAC (1,200 mg/d) for 12 months significantly reduced COPD acute exacerbation. A meta-analysis summarized 30 RCT studies with 7,436 COPD or chronic bronchitis patients. The results showed that NAC or carbocysteine reduced acute exacerbation by 17%,<sup>47</sup> suggesting that oral intake of mucoactive medicines may reduce acute exacerbation. The PANTHEON<sup>6</sup> study enrolled 1,297 COPD patients from 34 hospitals in the People's Republic of China; among those patients, 1,006 were randomly assigned to control NAC (600 mg bid [twice a day]) and placebo groups. After 1 year follow-up, the results showed that NAC significantly reduced acute exacerbation, especially in moderate COPD patients with high tolerance to NAC.

Zheng et al<sup>5</sup> followed 709 COPD patients for 1 year (PEACE study) and found that there was a 24% decrease of acute exacerbation in COPD patients who received carbocysteine (0.5 g, tid [thrice a day]; treatment group) compared to the placebo group. Allegra et al<sup>48</sup> investigated 662 chronic bronchitis patients treated with carbocysteine lysine salt for 1 year. Among those patients, in the continuous treatment group (2.7 g/d for 6 months), only 66 patients (29%) had >1 acute exacerbations, while 100 patients in the intermittent treatment group (2.7 g/d, every other week) had >1 exacerbations.<sup>48</sup> The treatment group showed significantly delayed onset of first acute exacerbation. Compared to the placebo group, the continuous treatment group had fewer days of acute exacerbation, while no difference was found between the intermittent group and the placebo group in terms of acute exacerbations. These results suggest that continuous and long-term treatment with carbocysteine may provide meaningful clinical outcome for COPD acute exacerbation.

In 2004, a multiple-center double-blinded placebo control and long-term study<sup>49</sup> using erdosteine in COPD patients showed that erdosteine (300 mg bid for 8 months) could significantly reduce acute exacerbation and hospitalization

while increasing the lung function and quality of life compared to the placebo group.

COPD patients (n=242) with percent predicted FEV<sub>1</sub> (FEV<sub>1</sub>%pred) between 60% and 80% were enrolled in a 1-year study with two arms; one arm used ambroxol (75 mg, bid) and one arm used placebo.<sup>50</sup> After 6 months, 63% patients from the treatment group and 60% patients from the placebo group did not have acute exacerbation, and the ratio decreased to 56% and 53% after 1-year follow-up, respectively. Among the patients who had the worst clinical score, 63% patients in the treatment group and 38% patients in the placebo group did not have acute exacerbation. This study showed that ambroxol application may have benefit in those COPD patients who had more severe symptoms. This evidence suggests that the 4 medicines listed in this review did reduce acute exacerbation in COPD to different extents, although dosing and duration are different.

## Mucoactive/antioxidant drugs could improve symptoms and quality of life

In addition to reducing acute exacerbation in COPD, mucoactive/antioxidant therapy could also decrease cough with sputum and hospitalization. Results from the PANTHEON study<sup>6</sup> showed significant improvement in clinical symptoms after 1-year treatment with NAC. In the PEACE<sup>5</sup> study, the St George's Respiratory Questionnaire (SGRQ) scores were significantly decreased in the carbocysteine group (4.06), compared to the placebo group, especially their symptoms and activity. In the EQUALIFE<sup>49</sup> study, the SGRQ score was significantly improved in the erdosteine treatment group, while no SGRQ score changes were found in the placebo group. However, results from these studies were not consistent with each other. In the BRONCUS<sup>45</sup> study, there was no difference in the SGRQ scores between the treatment and control groups after 1-year treatment, and there was no improvement in the quality of life with NAC therapy in the second year. In the HIACE<sup>46</sup> study (NAC 600 mg, bid), mMRC, SGRQ and 6 min walk distance did not show significant differences between treatment and placebo groups. In the PANTHEON study,<sup>6</sup> although NAC (600 mg, bid) could reduce SGRQ ( $-3.37$ ,  $P=0.043$ ), overall SGRQ and other scores were not different from the placebo group.

An RCT study conducted in Europe using erdosteine suggested that erdosteine could effectively reduce acute exacerbation in chronic bronchitis patients, improving clinical symptoms including cough, expectoration and dyspnea.<sup>51</sup> Acute exacerbated chronic bronchitis patients (n=226) were enrolled in this study, with the treatment group taking erdosteine 300 mg tid for 7–10 d while both treatment group

and control group used amoxicillin 50 mg tid. Results showed that average clinical evaluation performances, including objective and subjective clinical symptom improvement, lung function and sputum properties, were improved in 60% of the treatment group, while only 41% in the control group showed improvement. Another double-blinded study conducted in France enrolled 170 stable chronic bronchitis patients, with the treatment group taking erdosteine 300 mg bid for 21 d. Results showed that erdosteine decreased the global effective index by 27%, while only 19.2% reduction was found in the placebo group.<sup>52</sup> The most prominent parameters with significant improvement were frequency and severity of cough. Within 10 d of treatment, erdosteine significantly decreased the sputum viscosity (−22.9% vs −10.8%;  $P < 0.05$ ) and improved the cough index (−19.3% vs −10.4%;  $P < 0.05$ ), respectively. Maximum ventilation capacity was also significantly improved in the treatment group.

### Mucoactive/antioxidant drugs can decrease hospitalization and hospital time

In the HIACE study,<sup>46</sup> there was a trend showing declined hospitalization rate in the NAC group compared to placebo (0.5/year vs 0.8/year), as well as hospitalization days (1.8 d/year vs 4.2 d/year); however, there was no statistical difference. Gerrits et al<sup>53</sup> separated 1,219 COPD patients (>55 years old) into NAC group and non-NAC group, comparing their first acute exacerbation and hospitalization. Results showed that 30% rehospitalization was reduced in the NAC group and there was a reversed dose–response correlation between NAC dose and hospitalization, with less hospitalization at high doses of NAC ( $P < 0.0001$ ). Moretti et al<sup>49</sup> reported in the EQUALIFE study that hospitalization times and averaged hospitalization days were significantly reduced in the erdosteine group after 8-month treatment.

### Mucoactive/antioxidant drugs can partially improve lung function

Flow limitation is mainly caused by small airway disease and lung parenchyma damage (emphysema). Chronic inflammation induces small airway structural changes, with reduction in the number of alveoli attached to the small airways, thus resulting in decreased lung elasticity. NAC has anti-inflammatory and antioxidant properties, decreasing distal space air retention and improving exercise endurance.<sup>54</sup> An RCT study by Stav and Raz<sup>55</sup> found reduced hyperinflation after 6-week treatment with NAC (1,200 mg/d) in moderate-to-severe COPD patients (aged >40 years,  $FEV_1 < 58\%$  pred, residual capacity to total lung capacity [RC/TLC] >137%, inspiratory capacity [IC] >2.2 L),

including increased IC, free light chains (FLCs) after exercise, and decreasing RC/TLC after exercise. The decreased airway resistance and hyperinflation effects were also confirmed in the HIACE study,<sup>46</sup> suggesting that NAC could significantly improve small airway function.

In the BRONCUS study,<sup>45</sup> there was a 54 mL decrease of  $FEV_1$  after NAC treatment, with a 47 mL decrease in the placebo group; there was no statistical difference.  $FEV_1$ , forced vital capacity (FVC), and  $FEV_6$  were not changed between NAC and placebo groups in the PANTHEON<sup>6</sup> study. No improvement in lung function and oxygen saturation was found in the PEACE<sup>5</sup> study after carbocysteine treatment. Although Moretti<sup>38</sup> found that erdosteine treatment improved  $FEV_1$ , the baseline of  $FEV_1$  was high in the treatment group (200 mL more). If this difference was subtracted, there was no  $FEV_1$  change after expectorant therapy in the EQUALIFE<sup>49</sup> study. The possible explanation could be that expectorant/antioxidant medicines are not bronchodilators and  $FEV_1$  may not be the best indicator for COPD improvement; however, in moderate-to-severe COPD patients, reduced airway trapping and small airway function improvement may contribute to symptom improvement.

### Effects of mucoactive/antioxidant drugs on the whole system and acute exacerbation

COPD is a traditional respiratory disease but with systemic involvement, including muscle atrophy, osteoporosis, exercise capacity, fat loss, etc.<sup>56,57</sup> NAC reduces fatigue in healthy volunteers and delays fatigue duration.<sup>58,59</sup> Stav and Raz<sup>55</sup> found that treatment with NAC 1,200 mg for 6 weeks could increase exercise time, while in the HIACE<sup>46</sup> study, such improvement was not confirmed. Zuin et al<sup>60</sup> found that both NAC 1,200 mg/d or 600 mg/d could improve symptoms related to acute exacerbation, such as cough with sputum, dyspnea, and lung function decline; the higher the dose used, the better was the outcome.

Wang et al<sup>61</sup> studied the effects of ambroxol on AECOPD. Eighty COPD patients were randomly assigned into 2 groups, with the treatment group using intravenous ambroxol at 120 mg daily for 10 d. Absolute changes in IL-8, IL-10, TNF- $\alpha$ ,  $FEV_1\%$ pred and  $FEV_1/FVC$  were significantly greater after ambroxol treatment, suggesting that large doses of ambroxol may have anti-inflammatory effects that facilitate lung function recovery.

### Minimal side effects

Overall, there were few side effects in clinical studies using expectorant/antioxidant medicines. In the HIACE<sup>46</sup> study,

large doses of NAC did not bring about severe side effects. Long-term use of NAC (600 mg, 1 year) has been proved safe and tolerable, without significant difference in terms of side effects between treatment group and placebo group. In the PANTHEON study,<sup>6</sup> 146 out of 495 (29%) in the NAC group showed mild side effects, not different from the control group (130 out of 495, 26%). In addition, the major side effects such as acute exacerbation should be irrelevant to NAC application. High doses of NAC (1,800 mg/d) in clinical trials on idiopathic pulmonary fibrosis also showed good tolerance to NAC.<sup>62</sup>

## Existing problems in these studies

There are several limitations that should be considered when interpreting these results. First, the major problem is the limited sample sizes. Except PEACE,<sup>5</sup> PANTHEON<sup>6</sup> and the BRONCUS<sup>45</sup> studies with sample size more than 500, most other studies only enrolled small number of patients, thus making the overall level of evidence lower. Second, the reviews or meta-analyses were mostly written in Chinese. Third, except the PEACE,<sup>5</sup> PANTHEON,<sup>6</sup> BRONCUS<sup>45</sup> and HIACE<sup>46</sup> studies, treatment times were generally short, varying from few weeks to 6 months. The PEACE<sup>5</sup> and PANTHEON<sup>6</sup> studies have shown that the longer the treatment duration, the better is the outcome that the patients would have. The dose–response profile of NAC suggested that a high dose (1,200 mg/d) is required for confirmed benefit. Fourth, the target population needs to be assessed in future studies. Lastly, the BRONCUS<sup>45</sup> study showed that COPD patients without ICS use gain more benefit from NAC than those who use ICS. In the PANTHEON study, moderate COPD patients gained more improvement than severe COPD patients, suggesting that long-term and regular treatment is critical to gaining benefit in the early stages of COPD.

## Clinical application recommendations of mucoactive/ antioxidant medicines

### Expectorant/antioxidant medicine recommendation from COPD guidelines

GOLD 2013<sup>63</sup> indicated for expectorant/antioxidant medicine use for treatment of hypersecretion in COPD airway, as may induce recurrent infection and airway obstruction. Expectorants facilitate airway drainage and improve lung function but only work in patients who have mucus production. The frequently used medicines include ambroxol and NAC. The Chinese physician consensus on AECOPD (2014 revised version) proposed that NAC is effective in reducing acute exacerbation, especially in patients who do

not use ICS.<sup>64</sup> GOLD 2015 cited an article by Zheng et al<sup>6</sup> and recommended the long-term use of NAC (1,200 mg/d) in moderate-to-severe COPD patients to reduce acute exacerbation with/without ICS inhalation. The American College of Chest Physicians (ACCP)/Canadian Thoracic Society (CTS)<sup>65</sup> recommend oral intake of NAC in moderate-to-severe COPD patients to prevent acute exacerbation. For clinically stable COPD patients, NAC or carbocysteine should be used regularly to reduce exacerbation and improve quality of life. GOLD 2016 particularly pointed cough with sputum as an independent factor associated with increased mortality in mild-to-moderate COPD patients; this statement strongly suggested the importance of antitussive and mucoactive therapy in COPD patients.<sup>66</sup>

## Recommendations based on the cited studies and clinical practice

### Expectorant/antioxidant therapy in stable COPD

Long-term mucoactive/antioxidant therapy for chronic bronchitis or COPD patients should be initiated as long as patients complain of cough with sputum or dyspnea. If the patient with the evidence of COPD lung function complains of cough with sputum since childhood and if computed tomography (CT) scan shows evidence of bronchiectasis, patients do need mucoactive/antioxidant therapy. COPD patients whose FEV<sub>1</sub>% is more than 50% but who complain of cough with sputum, patients who have a problem sleeping due to expectoration symptom and asthma or allergy could be excluded. COPD patients with lung function classes 3 and 4, more than 2 clinical visits, and GOLD C or D group patients who do not have ICS inhalation or who show a combination with bronchiectasis need treatment.

### AECOPD

Few studies suggest that mucoactive/antioxidant therapy in AECOPD patients may provide additional benefit, and combining chest wall motion may propagate the airway clearance benefit.<sup>49</sup>

### Usage

There are many mucoactive medicines in clinical practice; we summarized a few of them that have relatively clearer therapeutic indications based on RCT results. Herein, NAC, carbocysteine, and erdosteine have been recommended for anti-inflammation therapy in COPD patients. Due to lack of RCT trials, ambroxol is not recommended for long-term therapy at large doses, while as mucoactive therapy, ambroxol 75 mg bid has been recommended in COPD and chronic bronchitis patients. Being an anti-inflammatory medicine,

dose and duration are critical. NAC 1,200 mg/d, carbocysteine 1,500 mg/d and erdosteine 600 mg/d for 3–6 months are minimum regimes in COPD patients. For sole mucoactive therapy, this dose could be reduced in half. If patients cannot tolerate the 6-month regimen, they are recommended to try the treatment plan during the spring and winter, while persistent dosing in summer is recommended to reduce respiratory system symptom, COPD hospitalization and acute exacerbation.

Price is another concern during COPD treatment. The price of NAC in the People's Republic of China is around 1 USD per capsule, roughly 60 USD/mo. Ambroxol costs around 0.15 USD per tablet in the People's Republic of China, roughly 27 USD/mo; carbocysteine costs around 0.02 USD per capsule, roughly 3.6 USD/mo; for erdosteine, the price is around 0.9 USD per capsule, roughly 55 USD/mo. In general, the cost of antioxidant mucoactive therapy is roughly similar to or one-third to half the price of monthly used bronchodilators. Considering the fact that patients may need both bronchodilators and expectorants together, the cost-effectiveness should be borne in mind before prescription.

## Conclusion

COPD is a heterogeneous disease with complicated pathogenesis and treatment responses. Current evidence suggests that antioxidant expectorants may reduce airway inflammation, decrease oxidative stress, reduce acute exacerbation and improve quality of life in COPD patients. Precise treatments in targeted COPD population need further investigation with stratification strategy.

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## Disclosure

The authors report no conflicts of interest in this work.

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